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STUDY ON THE MECHANISM OF DERMATITIS VENENATA IN THE GUINEA PIG WITH A DEMONSTRATION OF SKIN-SENSITIZING ANTIBODY BY PASSIVE TRANSFER*†

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ALTHOUGH dermatitis venenata is classified as an allergic disease, the immunologic bases for this have stood on scant evidence. There have been occasional cases of passive transfer with serum, and Urbach[1] has reported similar success using blister fluid. This latter contains both serum and cellular fluid. In 1942, Landsteiner and Chase[2] demonstrated passive transfer of dermatitic sensitivity, using washed sterile exudate cells, in guinea pigs. However, these animals were sensitized by using hapten combinations and adjuvants intraperitoneally. Recently, Chase[3] demonstrated successful transfer of tuberculin sensitivity by using washed cells obtained from sterile exudates. This past year, in a lecture, he also reported transfer of dermatitic sensitivity in guinea pigs by similar methods.[4] Heretofore, the evidence upon which the allergic nature of dermatitis venenata was based was on indirect observations. Children who did not react to patch tests with poison ivy extract did so after several applications of the extract.[5] Similarly, eskimos[6] who had had no contact with poison ivy did not react. Again in the guinea pig,[7] it has been shown that animals that did not react to certain concentrations of poison ivy on patch tests did react, in a period of time, after several applications of similar strengths.

Because the previous work has so strongly suggested an immunologic basis for dermatitis venenata and because Chase's work with both tuberculin and 2′4′dinitrochlorobenzene also suggested a cellular rather than a humoral antibody, the following studies were made.

METHODS

White guinea pigs from two sources, fed on stock foods, were used throughout. All animals were clipped and the skin cleansed with a depilatory cream. Then one drop of 5 per cent poison ivy extract in absolute alcohol (this strength of extract was found nonirritating) was placed on the skin. Twenty-four hours later the extract was removed with acetone. A similar dose of poison ivy was placed on the same skin site every other day, and at the end of ten days definite

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evidence of skin irritation was noted in that in the area of the patch the skin became red and mildly edematous. The reaction appeared in twelve hours and generally lasted twenty-four to forty-eight hours. Following this demonstration of direct sensitization, the animals were anesthetized with ether and bled from the heart. The spleen was then removed, cut into small pieces, and placed in physiologic saline. Gentle pressure on the spleen sections squeezed the splenic cells out into the saline. By gentle agitation a reasonable suspension of splenic cells was obtained. This suspension was centrifuged and the saline siphoned off. The cells were washed three times to remove the serum and the last wash water saved for control. Splenic cells, rather than sterile exudate cells, were chosen for use because of the high content of reticulo-endothelial cells and the readiness with which a suspension of these cells could be obtained.

Then, normal white guinea pigs were patch tested and readings were made in twenty-four hours. No animals reacted, and they were then given an injection of either serum, splenic cells, or the wash water obtained from the splenic cells. Twenty-four hours later they were again patch tested at a different site and readings were made in another twenty-four hours. The results are noted in Table I. In seven of fifteen trials serum passively transferred mild sensitivity. In sixteen of nineteen trials the splenic cells transferred a much more marked dermatitic reaction. In only one instance did the third wash water obtained from the splenic cells transfer sensitivity.

TABLE I. STUDIES ON PASSIVE SENSITIZATION OF GUINEA PIGS TO POISON IVY

DONOR GUINEA PIG SENSITIVE TO POISON IVY	PATCH TEST*	RESULTS OF PATCH TESTS ON RECIPIENT GUINEA PIGS		
		GUINEA PIG† INJECTED WITH 2 C.C. SERUM	GUINEA PIG† INJECTED WITH WHOLE SPLENIC CELLS	GUINEA PIG† INJECTED WITH THIRD WASH WATER FROM SPLENIC CELLS
1	++		0	0
3	++	0	++	0
4	++	0	++	0
5	+++	+	++±	0
6	+++	+	++	0
7	++	+	++	0
8	++	+	++	0
9	++	+	+	0
11	++		±	0
12	+		+	0
13	++	0	++	±
14	++		+	0
92	+++	++	++±	0
32	+	+	++	-
67	+	±	+	0
68	+	0	+	+
62	++	0	+	0
125	++	+	+	0

0, No reaction; ±, ? redness; +, slight but definite redness; ++, moderate redness with edema; +++, marked redness and edema.

*Animals were patch tested by clipping hair close to skin and applying one drop of a 5 per cent absolute alcohol extract to the area. Twenty-four hours later the area was cleansed with a depilatory cream and excess poison ivy removed with acetone. Initial readings were made two to three hours later and again in twenty-four hours. The maximum reaction is recorded.

†Recipient animals for the passive transfer tests were first patch tested as described and readings made in twenty-four hours; all were negative. Then each animal was injected intraperitoneally with serum or splenic cells or wash water. They were again patch tested in twenty-four hours with readings as recorded above.

TABLE II. STUDIES OF PASSIVE SENSITIZATION OF GUINEA PIGS WITH EXTRACTS OF SPLENIC CELLS

DONOR GUINEA PIG SENSITIVE TO POISON IVY	PATCH TEST*	RESULTS OF PATCH TESTS ON RECIPIENT GUINEA PIGS		
		GUINEA PIG† INJECTED WITH 2 C.C. SERUM	GUINEA PIG† INJECTED WITH EXTRACT OF WASHED SPLENIC CELLS	GUINEA PIG† INJECTED WITH THIRD WASH WATER FROM WHOLE SPLENIC CELLS
2	++	0	++	0
70	++	+	+±	0
65	++	±	0	0

0, No reaction; ±, ? redness; +, slight but definite redness; ++, moderate redness with edema; +++, marked redness and edema.

*Animals were patch tested by clipping hair close to skin and applying one drop of a 5 per cent absolute alcohol extract to the area. Twenty-four hours later the area was cleansed with a depilatory cream and excess poison ivy removed with acetone. Initial readings were made two to three hours later and again in twenty-four hours. The maximum reaction is recorded.

†Recipient animals for the passive transfer tests were patch tested as described and readings made in twenty-four hours; all were negative. Then each animal was injected intraperitoneally with serum or splenic cells or wash water. They were again patch tested in twenty-four hours with readings as reported above.

In three trials, the spleens were washed three times as previously. The suspensions of cells were then dried in a cryochem apparatus and an extract of the dried material was made. Ten cubic centimeters of saline per gram of dried material were added to the dried cells and the mixture placed in the ice box for twenty-four hours. Then the mixture was centrifuged and the supernatant fluid pipetted off. This supernatant was used for passive transfer experiments similar to those previously described and with the results shown in Table II. In two of three trials the extract transferred sensitivity. In all cases serum gave either a negative or a positive passive transfer less intense than that obtained using splenic cells.

Splenic cells and serum obtained from three normal guinea pigs did not transfer sensitivity to poison ivy.

Female guinea pigs, all positive to patch test with poison ivy, were then mated with a male who was also poison ivy sensitive. Patch tests on the mothers were performed periodically during gestation and all were positive at the time of the delivery of their young. Four baby guinea pigs were patch tested in the usual way when they were three days old and all were negative. Repeated applications of poison ivy to the skin three times a week were sufficient to sensitize the animals in ten days. (Table III.)

TABLE III. RESULTS OF STUDIES OF PLACENTAL TRANSFER OF DERMATITIC SENSITIVITY

FATHER GUINEA PIG SENSITIVE TO POISON IVY BY PATCH TEST	MOTHER GUINEA PIG SENSITIVE TO POISON IVY BY PATCH TEST	FINAL PATCH TEST OF MOTHER AT DELIVERY	BABY GUINEA PIG	BABY GUINEA PIG PATCH TESTS*	
				INITIAL PATCH TEST ON THIRD DAY OF LIFE	AFTER REPEATED TEST TEN DAYS LATER
54	70	++	1st	0	+
			2nd	0	++
	62	++	1st	0	+
72	110	+	1st	0	++

0, No reaction; ±, ? redness; +, slight but definite redness; ++, moderate redness with edema; +++, marked redness and edema.

*Animals were patch tested by clipping hair close to skin and applying one drop of a 5 per cent absolute alcohol extract to the area. Twenty-four hours later the area was cleansed with a depilatory cream and excess poison ivy removed with acetone. Initial readings were made two to three hours later and again in twenty-four hours. The maximum reaction is recorded.

COMMENT

The previously cited work[2-4] has suggested that dermatitis due to contact with simple chemical substances was mediated by a cellular antibody. Sensitivity to alcoholic extracts of poison ivy produced by cutaneous application of the antigen falls into the same category. The antibody in this type of sensitivity appears to be a cellular one which can be isolated from the cells by saline extraction. It would also seem that occasionally small amounts of antibody may appear in the blood serum although it is possible that the positive sera may contain some intracellular material derived from cells broken up in the process of collecting the serum. The successful passive transfer of dermatitic sensitivity, using whole splenic cells or extracts thereof, suggests that other tissues of the body and not just the skin contain antibodies and can therefore be sensitized by cutaneous application of antigenic material. Previous work on the origin of antibodies has shown that the lymph nodes play an important part in the formation of antibodies.[8] This would also afford a rational explanation for the content of dermatitic sensitizing antibody in the splenic cells. If one accepts the role that these cells play in the producing and storing of antibodies, then the explanation for the diffuseness of the sensitivity in spite of application of antigen to a localized area of skin is readily available. The extensive study of Chase[9] and the present study also indicate that dermatitic sensitivity does not appear to be transferred from the mother to her offspring via the placenta.

SUMMARY

1. Guinea pigs were sensitized to poison ivy extract by cutaneous application of the antigen.

2. Successful passive transfer of dermatitic sensitivity was obtained in seven of fifteen trials with serum and sixteen of nineteen trials with a suspension of splenic cells. Reactions caused by serum were slight.

3. The dermatitic antibody could be demonstrated in saline extracts of washed splenic cells.

4. The dermatitic antibody did not pass through the placenta.

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DISCUSSION

DR. MAX GROLNICK, Brooklyn, N. Y.—In considering the results just presented it is well to bear in mind the statement by Landsteiner in his recent text, that although guinea pigs lend themselves well to experiments in sensitization with chemicals, such sensitivity never reaches a degree comparable to that of highly allergic individuals. Earlier investigators in poison ivy sensitization in the guinea pig (Simon, Straus, Simon, Simon, Rackman, and Dienes, Ginsberg, Becker, and Becker) have called attention to the initial skin irritation caused by the first application of poison ivy extract. In the report just presented a nonirritating concentration of the excitant has been employed.

In the earlier literature on passive transfer of sensitivity of the eczematogenous or contactant type, whether from human being to human being, from human being to animal, or from animal to animal, no clear demonstration of transfer by serum is available. The contents of blister fluid likewise failed in this respect (Sulzberger and Katz, Pratt and Carson). Simon could not show transfer by means of blood transfusion from sensitive to nonsensitive animal.

In a somewhat analogous situation, namely, tuberculin sensitivity, Corper and Cohen failed to transfer sensitivity by the intravenous injection of citrated whole blood. Chase was likewise unsuccessful in transferring serum from the sensitive to the nonsensitive animal. The presence of a humoral antibody would seem to be negated by this evidence.

The present report showed a transfer of epidermal-type sensitivity to poison ivy with the use of serum in 46 per cent of the animals, a finding not previously demonstrated.

In regard to the tissue cell as the source of antibody, the authors employed the splenic cell rather than peritoneal exudate cells, as used by Landsteiner and by Chase. Their procedure was a simpler one than that of the latter investigators and demonstrated an 84 per cent incidence of transfer.

Concerning technique, I feel that a control group of animals which were not prepatched with poison ivy would have given weight to the conclusions of the authors. It is true that the experiments were completed in a seventy-two hour period, an interval generally considered as too short for inducing sensitivity, although very close to the limit of incubationary period for sensitization in the guinea pig. The prepatch, theoretically and actually, is known to initiate a sensitizing process. Although three controls were done with splenic cells from nonsensitive animals, it is not clear in the description of the technique whether or not prepatched animals were used. A larger control series would have been desirable.

Finally, the authors, like Chase, failed to show transfer in animals of sensitivity from mother to offspring. Similar findings were obtained previously (Grolnick) in pregnant mothers sensitized with Krameria in the latter trimesters of pregnancy.

Original Articles

EXPERIMENTS ON HISTAMINE REFRACTORINESS

III. The Effect of Histamine Pretreatment on the Establishment of Active Sensitization*†

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PRETREATMENT of serum-sensitized guinea pigs with histamine induces decreased anaphylactic response in these animals. This was shown by Farmer[1, 2] using the Schultz-Dale technique and later by Karady[3] in the intact animal. In Farmer's experiments histamine pretreatment was instituted at the height of sensitization. In Karady's work it was carried out before, during, and through the sensitization period.

It was concluded from these experiments that the lesser degree of anaphylactic reactivity is due to increased histamine tolerance and these experiments were interpreted as providing further indirect evidence of the correctness of the histamine theory of anaphylaxis. As an alternative explanation one could assume that the decreased anaphylactic response is due to interference with the immunologic process, i.e., that histamine pretreatment leads to a lesser degree of anaphylactic sensitization.

Passive sensitization experiments should further clarify these questions. By carrying out the anaphylactic experiment in passively sensitized "normal" guinea pigs, i.e., guinea pigs which had not been pretreated with histamine but which had been passively sensitized with the serum of (a) actively sensitized normal guinea pigs and (b) actively sensitized and histamine-pretreated guinea pigs, it would be possible to ascertain if histamine pretreatment had exerted an effect on the establishment of active sensitization.

EXPERIMENTAL

I. Control Experiments.—Male guinea pigs, weighing on an average from 180 to 250 grams, were actively sensitized by one intraperitoneal injection of 0.5 c.c. normal horse serum diluted 1:10. Twenty-one days later the animals were bled from the heart, the serum was pooled and thirty-four normal male guinea pigs, weighing on an everage from 200 to 300 Gm., were each passively sensitized by an intraperitoneal injection of 5.0 c.c. of this serum. Twenty-four hours later these animals were given an intravenous injection of 0.4 c.c. normal horse serum. Eight animals, or 23.5 per cent, died in shock.

II. Histamine Phosphate Pretreatment Experiments.—Male guinea pigs, weighing on an average from 180 to 250 grams, were actively sensitized by one

*From the Allergy Clinic and Achelis Laboratory, Lenox Hill Hospital.
†Aided by a grant from Parke, Davis & Co., Detroit, Mich.

intraperitoneal injection of 0.5 c.c. normal horse serum diluted 1:10. Histamine pretreatment was instituted the next day, according to the schedule used by Karady. The animals received a total of thirteen intraperitoneal injections of histamine acid phosphate over a period of 19 to 20 days. The first seven injections of 5, 10, 20, 40, 60, 80, and 100 γ per 100 Gm. of body weight were given on successive days. The eighth to thirteenth injections, which were 100γ per 100 Gm. of body weight each, were given at one to two day intervals. Two days after the last histamine injection, or twenty-one or twenty-two days after the sensitizing injection, the animals were bled from the heart and the serum was pooled. Each of thirty-seven normal guinea pigs, weighing on an average from 230 to 330 Gm., were passively sensitized by an intraperitoneal injection of 5.0 c.c. of this serum. Twenty-four hours later these animals were given an intravenous injection of 0.4 c.c. normal horse serum. Seven guinea pigs, or 18.9 per cent, died in shock.

III. Histamine Azoprotein Pretreatment Experiments.—Male guinea pigs, weighing on an average from 180 to 250 grams, were actively sensitized by one intraperitoneal injection of 0.5 c.c. normal horse serum diluted 1:10. Beginning the next day the animals were given thirteen intraperitoneal injections of histamine azoprotein at intervals of one to three days. In the first two groups of animals, undiluted histamine azoprotein was used. The guinea pigs did not tolerate the injections well and I later used 1:10 and 1:100 dilutions. Varying amounts of histamine azoprotein were given. In the first group of animals 0.47 c.c. per 100 Gm. of body weight, and in the second group 0.22 c.c. per 100 Gm. of body weight were used. The mortality rate in both of these groups was very high. I therefore reduced the total amount of histamine azoprotein used for pretreatment to 0.20 c.c. per 100 Gm. of body weight. This amount was given in a 1:100 dilution. Twenty-four hours after the last histamine azoprotein injection the animals were bled from the heart, their serum was pooled, and thirteen normal male guinea pigs, weighing from 220 to 320 grams, were passively sensitized by an intraperitoneal injection of 5.0 c.c. each of this serum. Twenty-four hours later these animals were given an intravenous injection of 0.4 c.c. normal horse serum. Three guinea pigs, or 23 per cent, died in shock.

TABLE I

CONTROL EXPERIMENTS			HISTAMINE PHOSPHATE PRETREATMENT			HISTAMINE AZOPROTEIN PRETREATMENT		
TOTAL ANIMALS SHOCKED	FATALITIES		TOTAL ANIMALS SHOCKED	FATALITIES		TOTAL ANIMALS SHOCKED	FATALITIES	
	NO.	%		NO.	%		NO.	%
34	8	23.5	37	7	18.9	13	3	23

SUMMARY AND CONCLUSION

Table I summarizes the results of all experiments. It shows that the percentage of fatalities was virtually the same in the three groups of animals which were passively sensitized by the serum (a) of sensitized "normal" guinea pigs, (b) of sensitized guinea pigs pretreated with histamine phosphate,

and (c) of sensitized guinea pigs pretreated with histamine azoprotein. This indicates that pretreatment with histamine phosphate or histamine azoprotein did not interfere with the establishment of active sensitization. One may, therefore, conclude that the lesser degree of anaphylactic reactivity which was observed by Farmer and Karady in sensitized and histamine-pretreated guinea pigs was due to increased histamine refractoriness.

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EXPERIMENTS ON HISTAMINE REFRACTORINESS

IV. Histamine Pretreatment in Eggwhite-Sensitized Guinea Pigs*†

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IN EARLIER experiments Farmer[1, 2] showed that uterine strips of serum-sensitized guinea pigs which had received histamine orally or by intraperitoneal injections were less sensitive to the antigen than were the control animals which had not been pretreated with histamine.

Karady[3] confirmed these findings in the intact animal. Anaphylactic death in serum-sensitized guinea pigs which had been pretreated with histamine could be prevented in 75 to 90 per cent of the animals in contrast to only 15 to 25 per cent survival in the controls.

However, Karady found that if eggwhite was used as the sensitizing antigen pretreatment with histamine did not significantly protect the animals from fatal anaphylaxis. In contrast to this finding, Karády and Bentsáth[4] have reported that in eggwhite-sensitized and histamine-pretreated guinea pigs a lesser drop in rectal temperature was observed on reinjection with the specific antigen than in the control animals. This observation was interpreted by Karády and Bentsáth as demonstrating that the histamine-pretreated animals showed a lesser degree of anaphylactic response.

It would seem that the different outcomes of the anaphylaxis experiments in serum- and eggwhite-sensitized guinea pigs after histamine pretreatment (Karady,[3]) are based on quantitative factors rather than on fundamental differences of mechanism. We subscribe to Karady's opinion that: "A possible explanation . . . lies in the fact that guinea pigs are very easily highly sensitized to eggwhite so that even minute amounts will release histamine in excess of the amount which treated animals will tolerate."

In view of the conflicting findings of Karady[3] and of Karády and Bentsáth[4] and because of the theoretic importance of the problem, the following experiments were undertaken.

EXPERIMENTAL

A. Technique.—In order to obviate the possibility of an interference with the immunologic process through histamine pretreatment, passive sensitization of the test animals was believed to be the method of choice.[5] Anti-eggwhite rabbit serum, prepared according to the method of Grove,[6] was used for passive sensitization. Two antiserums (III and V) were used. Serum V was divided into two parts (V_1 and V_2). The serums which varied in their sensitizing capacity (see Table II) were frozen, stored at –17° C., and thawed out before use.[7]

*From the Allergy Clinic and Achelis Laboratory, Lenox Hill Hospital.
†Aided by a grant from Parke, Davis & Co., Detroit, Mich.

TABLE I. HISTAMINE PRETREATMENT EXPERIMENTS

GUINEA PIG	HORN	INITIAL EGGWHITE CONCENTRATION	EGGWHITE CONCENTRATION AT WHICH CONTRACTION OCCURRED	REACTION
		Rabbit Serum III		
1882	1	$1:10^{7}$	$1:10^{4}$	+++
	2	$1:10^{6}$	$1:10^{2}$	+++
1883	1	$1:10^{6}$	$1:10^{6}$	+++
	2	$1:10^{8}$	$1:10^{2}$	+++
1885	1	$1:10^{7}$	$1:10^{2}$	+++
	2	—	$1:5\times10^{1}$	Spontaneous
1886	1	$1:10^{7}$	$1:10^{4}$	+++
	2	$1:10^{6}$	$1:10^{6}$	+++
1887	1	$1:10^{7}$	$1:10^{6}$	+++
	2	—	—	Spontaneous
1876	1	—	—	Spontaneous
	2	$1:10^{7}$	$1:10^{7}$	+ (+)
1877	1	$1:10^{7}$	$1:10^{6}$	++
	2	—	—	Spontaneous
		Rabbit Serum V₂		
1894	1	—	—	Spontaneous
	2	$1:10^{7}$	$1:10^{7}$	++
1895	1	$1:10^{7}$	$1:10^{7}$	+
	2	—	—	Spontaneous
1896	1	$1:10^{7}$	$1:10^{6}$	++
	2	$1:10^{7}$	$1:10^{7}$	+++
1934	1	—	—	Spontaneous
	2	$1:10^{9}$	$1:10^{8}$	++
1937	1	$1:10^{9}$	$1:10^{7}$	++ (+)
	2	$1:10^{9}$	$1:10^{9}$	+++
1938	1	$1:10^{10}$	$1:10^{9}$	+++
	2	$1:10^{10}$	$1:10^{8}$	+
1939	1	$1:10^{10}$	$1:10^{10}$	+++
	2	$1:10^{10}$	$1:10^{10}$	++
1941	1	$1:10^{10}$	$1:10^{10}$	+++
	2	$1:10^{11}$	$1:10^{11}$	+++
1942	1	$1:10^{13}$	$1:10^{12}$	+++
	2	—	—	Spontaneous

The test animals, young virgin guinea pigs, weighing approximately from 200 to 300 grams, were passively sensitized by an intraperitoneal injection of 1.0 c.c. of antiserum diluted 1:5. Twenty-four hours later the animals were killed by a blow on the head and their uterine strips suspended in a Schultz-Dale bath as described in earlier publications.[1, 2] Frequently the horns showed spontaneous contractions on suspension in the bath; these horns were excluded from further examination.

If they remained relaxed the degree of their anaphylactic reactivity was determined by adding increasing amounts of fresh filtered eggwhite to the bath at intervals of one and one and one-half minutes until a contraction of the uterine strip was elicited. If no contraction occurred after addition of the eggwhite, 0.5 c.c. of a 1:1000 histamine phosphate solution was added to ascertain if the muscle was still reactive. In some of the histamine azoprotein experiments, 0.5 c.c. histamine azoprotein instead of histamine was added to the bath.

In numerous instances greatly varying amounts of eggwhite were needed to effect anaphylactic contraction of the individual uterine horns of the same animal. Results were therefore recorded and evaluated on the basis of the anaphylactic response of the individual uterine horn. The results of all experiments are given in Table II.

No attempt was made to express the results of these experiments in strictly quantitative terms as each subliminal dose of antigen will cause some degree of desensitization without eliciting a contraction of the uterine strip. In evaluating the experiments only the ranges in which contractions in the control and histamine pretreatment series occurred were compared.

B. Results.—

Control Experiments: Seventy-nine guinea pigs were passively sensitized and their anaphylactic reactivity determined as already described. (See Table II.)

TABLE II

EGGWHITE CONCENTRATION	CONTROL EXPERIMENTS	HISTAMINE PHOSPHATE PRETREATMENT	HISTAMINE AZOPROTEIN PRETREATMENT
1×10^{-18}	×		
1×10^{-17}	×		
1×10^{-16}	×		
1×10^{-14}	×××		
1×10^{-13}	××××		
1×10^{-12}	×	×	
1×10^{-11}		×	
1×10^{-10}		×××	
1×10^{-9}	×	×××	
1×10^{-8}	×××× +	××	×
1×10^{-7}	×××× 0	×× 0	×
1×10^{-6}	×× 000000000	× 0000	×
1×10^{-5}	×× 00000+++++++	×	×
1×10^{-4}	××××× 0000++	00	× ++++
1×10^{-3}	0		× ++
1×10^{-2}	00	00	××× ++

Eggwhite concentration is the amount of eggwhite needed to elicit contraction of the uterine strip.

0, Contraction of a uterine strip of an animal sensitized with serum III.
x, Contraction of a uterine strip of an animal sensitized with serum V_1.
+, Contraction of a uterine strip of an animal sensitized with serum V_2.

Histamine Phosphate Pretreatment Experiments: Sixty-six guinea pigs were used. They were given thirteen intraperitoneal injections of histamine phosphate in increasing amounts over a period of two weeks. The highest average dose given was 100 γ per 100 Gm. of body weight. In a few instances up to 150 γ per 100 Gm. was used. The total amount of histamine phosphate given was 1,085 γ per 100 Gm. of body weight. This amount was seemingly not well tolerated as 30 per cent of the animals died before they could be used for passive sensitization. Two or three days after the last histamine injection the animals were passively sensitized and twenty-four hours later their uterine strips were tested as has been described. (See Table II.)

Histamine Azoprotein Pretreatment Experiments: Forty guinea pigs were used in this group. They received thirteen intraperitoneal injections of histamine azoprotein in increasing amounts over a period of two weeks. Varying

amounts of histamine azoprotein were used for pretreatment. First, a total of 3.26 c.c., then, 0.61 c.c., and finally, 0.20 c.c. per 100 Gm. of body weight were given. The larger amounts of undiluted histamine azoprotein were very poorly tolerated so that recourse was taken to a 1:10 and a 1:100 dilution. The percentage of fatalities in the histamine azoprotein group was 62 per cent so that only fifteen pretreated animals survived. Two or three days after the last histamine azoprotein injection the animals were passively sensitized and their uterine strips were tested twenty-four hours later. (See Table II.)

DISCUSSION

As appears from the table there is no appreciable difference in the amounts of eggwhite needed to effect contraction of the uterine strips of the control animals and of the animals pretreated with histamine phosphate or histamine azoprotein. This finding is in accordance with Karady's experiments with eggwhite sensitization. It is in contrast to our findings in guinea pigs sensitized with horse serum.

SUMMARY

Histamine pretreatment of guinea pigs (passively) sensitized to eggwhite failed to decrease their anaphylactic response to the specific antigen. This result is in contrast to our findings in serum-sensitized guinea pigs in which pretreatment with histamine decreases the anaphylactic response to serum.

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THE INFLUENCE OF INTRAVENOUSLY ADMINISTERED BENADRYL ON BLOOD PRESSURE AND ELECTROCARDIOGRAM*

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INDICATIONS for rapid action in transfusion reactions,[1] irradiation sickness,[2] serum sickness,[3] and penicillin sensitivity[4] frequently necessitate intravenous administration of so-called antihistamine drugs. The oral behavior of one of these, Benadryl Hydrochloride (beta-dimethylaminoethyl benzhydryl ether hydrochloride) is well known and has been abundantly publicized. The intravenous action of this drug, however, has not been investigated thoroughly and consequently confusion exists regarding the proper dosages and potential effects on the cariovascular system. This study was undertaken, therefore, to supply this information by recording the effects of intravenous injection of various amounts of Benadryl solution† on systemic reactions, blood pressure, and the heart as interpreted by the electrocardiogram.

MATERIAL AND METHODS

Thirty-five males and twenty females, ranging from 18 to 54 years of age were employed in this investigation. These subjects were mostly surgical patients who had no evidence of cardiovascular disease or histories of allergy. Before beginning the test, all patients were fasting and had abstained from smoking for at least six hours. All records were taken with the patient recumbent.

Control records, taken before injection, included pulse rates, blood pressures, and electrocardiograms, using the three classical limb leads and chest lead CR 4.

As additional controls, five patients were injected with 50 c.c. of distilled water and records taken as above. No systemic reactions or changes in either blood pressure readings or electrocardiograms were noted. Objections to the use of distilled water as a diluent for the Benadryl are on theoretic grounds only.

Ten patients were injected, respectively, with 50, 75, 100, 200, and 300 mg. of Benadryl. These individual amounts of the drug were mixed with sufficient distilled water to make 50 c.c. of solution. By means of a syringe, the solution was slowly injected in the anticubital vein for about four minutes.

Following injection, records of pulse rate, blood pressure, and electrocardiograms were taken at intervals of 5, 10, 15, 20, 30, 45, and 60 minutes.

RESULTS

The most common systemic reactions resulting from the above injections, in order of frequency, were dizziness, tingling of the hands and feet, sleepiness, difficulty with speech, indistinct vision, tremors, and nausea. In one or two cases, headache, flushing of the face, deep respiration, and hysteria were encountered.

*From the Department of Medicine, Germantown Dispensary and Hospital.
†Supplied through the courtesy of Parke, Davis & Co., Detroit, Mich.

Dizziness was the most common complaint. After 50 and 75 mg. of Benadryl this symptom was mild and transitory, rarely lasting twenty minutes. With larger doses, duration and severity of vertigo increased in proportion to the amount of drug used. After 300 mg. some of the patients complained of dizziness for the remainder of the day.

Tingling of the hands and feet was particularly prominent after 100, 200, and 300 mg. dosages. However, at the end of one hour all patients were free from this symptom.

Sleepiness was experienced by all patients after 100, 200, and 300 mg. of Benadryl. Several patients slept for short intervals during the test after having received 300 mg. and on being returned to the ward fell into sound slumber lasting several hours.

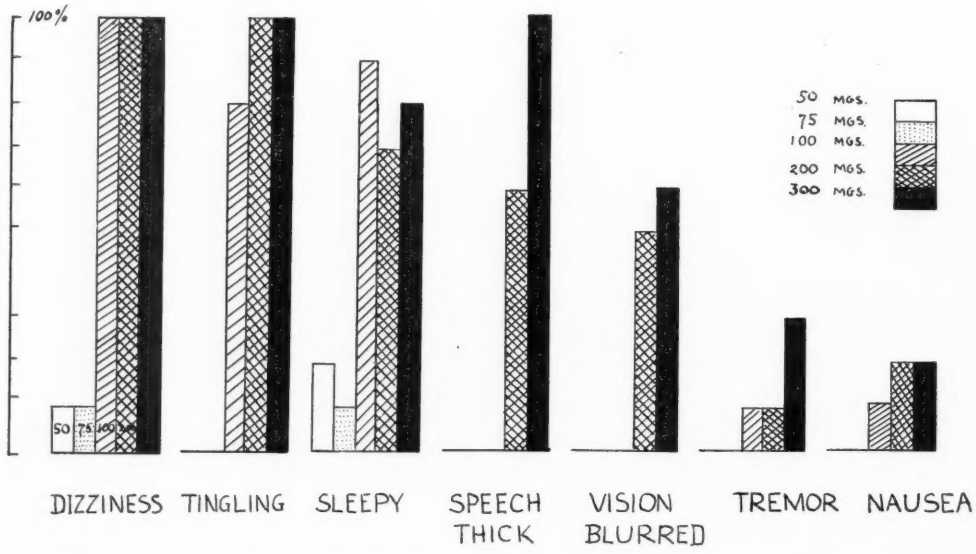

Fig. 1.—This graph records the frequency of the more important systemic reactions. Height of columns indicates the percentage number of subjects experiencing a particular reaction. No effort was made to indicate the duration of symptoms.

Slurring and difficulty with speech were present only after 200 and 300 mg. of the drug. Varying from simple hesitancy to definite anarthria, this finding was most prevalent five to thirty minutes after injection.

Blurred vision varied from simple distortion of objects to diplopia. Found only after administration of 200 and 300 mg. of Benadryl, this symptom lasted from five to forty-five minutes.

Tremors were occasionally experenced and varied from restlessness of hands or feet to generalized shaking of the body (in two patients).

Nausea of slight degree was demonstrated by many subjects after 200 and 300 mg. of the drug. Violent nausea occurred only in one patient after 300 milligrams. No vomiting resulted from any dose.

Slight supraorbital headache was found in one patient after receiving 100 mg. of Benadryl; flushing of the face was experienced by one patient after 300 mg.; and hysteria occurred in a woman after 200 milligrams.

EFFECT ON BLOOD PRESSURE

Average systolic and diastolic blood pressures were elevated after all doses of intravenously administered Benadryl. This rise was proportionate to the dosage. With 50 and 75 mg. of the drug, the blood pressures at the end of one hour were lower than the preinjection levels. However, with 100, 200, and 300 mg., the blood pressures not only remained higher at the end of the hour but remained elevated from 5 to 20 mm. for two hours or more.

TABLE I. EFFECT OF BENADRYL ON BLOOD PRESSURE

PATIENT	AGE	SEX	SYSTOLIC					DIASTOLIC				
			START	HIGH	LOW	INCREASE	DECREASE	START	HIGH	LOW	INCREASE	DECREASE
Distilled Water Controls												
A	48	M	120	128	122	8	0	80	84	76	4	4
B	18	M	120	118	110	0	10	74	74	62	0	12
C	36	FC	110	108	104	0	6	80	78	70	0	10
D	30	F	110	112	102	2	8	64	64	62	0	2
E	34	F	106	102	100	0	6	60	58	56	0	4
	Average change					2	6				.8	6
50 mg. Benadryl												
1	26	M	144	146	136	2	8	96	98	90	2	6
2	23	M	98	104	98	6	0	64	70	62	6	2
3	24	M	110	114	102	4	8	60	70	66	10	0
4	45	M	108	108	98	0	10	62	62	60	0	2
5	24	M	102	108	98	6	4	62	74	64	12	0
6	21	F	108	122	106	14	2	60	70	60	10	0
7	23	F	102	108	98	6	4	68	76	64	8	4
8	24	F	98	106	104	8	0	66	68	62	2	2
9	24	M	100	112	100	12	0	50	58	50	8	0
10	40	F	104	112	106	8	0	74	88	80	14	0
	Average change					7	4				7	2
75 mg. Benadryl												
11	26	M	98	108	102	10	0	64	76	70	12	0
12	24	M	118	118	112	0	6	64	78	68	14	0
13	33	M	114	108	96	0	18	68	78	68	10	0
14	29	M	110	128	120	18	0	68	82	70	14	0
15	29	M	106	118	108	12	0	74	82	78	8	0
16	27	M	98	102	92	4	6	62	74	62	12	0
17	48	M	146	148	136	2	10	80	90	86	10	0
18	41	M	116	120	114	4	2	72	80	74	8	0
19	47	M	92	100	92	8	0	58	68	62	10	0
20	31	M	116	120	112	4	4	72	80	74	8	0
	Average change					6	5				11	0
100 mg. Benadryl												
21	24	FC	118	128	120	10	0	58	78	66	20	0
22	17	F	128	132	118	4	10	52	80	58	28	0
23	22	M	110	122	102	12	8	58	80	60	22	0
24	51	F	130	170	142	40	0	70	88	70	18	0
25	23	FC	94	108	92	14	2	52	72	60	20	0
26	21	FC	108	124	112	16	0	64	78	66	14	0
27	23	FC	122	138	118	16	4	76	90	70	14	6
28	35	FC	118	138	122	20	0	72	80	70	8	2
29	42	M	116	134	124	28	0	80	84	80	4	0
30	25	M	106	120	114	14	0	74	88	76	14	0
	Average change					17	2.4				16	.8

(Table I cont'd on following page.)

TABLE I. EFFECT OF BENADRYL ON BLOOD PRESSURE (CONT'D)

PATIENT	AGE	SEX	SYSTOLIC					DIASTOLIC				
			START	HIGH	LOW	INCREASE	DECREASE	START	HIGH	LOW	INCREASE	DECREASE
						200 mg. Benadryl						
31	40	M	118	144	128	16	0	82	110	90	28	0
32	37	M	122	148	128	26	0	82	102	90	20	0
33	41	M	132	178	128	46	0	78	100	78	22	0
34	44	M	144	172	140	28	4	80	88	82	8	0
35	19	F	90	150	108	60	0	64	110	70	46	0
36	40	M	118	178	160	60	0	68	88	78	20	0
37	54	M	148	178	150	30	0	92	108	94	16	0
38	54	M	150	162	140	12	10	102	114	100	12	2
39	18	F	110	148	130	38	0	68	90	82	22	0
40	48	M	162	164	150	2	12	84	94	88	10	0
	Average change					32	2				20	.2
						300 mg. Benadryl						
41	45	FC	124	190	138	66	0	66	84	70	18	0
42	32	M	120	156	118	36	2	70	100	70	30	0
43	18	M	100	158	122	58	0	70	80	74	10	0
44	26	M	104	142	122	38	0	54	94	78	40	0
45	29	F	100	132	120	32	0	72	90	88	18	0
46	48	FC	144	198	170	54	0	76	104	88	28	0
47	21	M	114	160	138	46	0	60	110	84	50	0
48	24	M	124	142	138	18	0	52	98	84	46	0
49	43	M	132	160	140	28	0	78	110	100	32	0
50	34	F	118	150	118	32	0	70	96	80	26	0
	Average change					40.8	.2				29.8	0

C=colored patients; others not so designated are white patients.

As seen in Table I, there is no relation of the degree of elevation of blood pressure to either the preinjection level, sex, age, or medical condition of the patient. Elevations of both systolic and diastolic pressures depended only on the amount of the drug injected.

Control subjects receiving only distilled water had no significant alterations in either pulse rates or blood pressure.

Fig. 2 shows the distribution of the elevations of systolic and diastolic blood pressures at the time intervals of this experiment. Here will be noted that the initial increase in blood pressure was sustained over longer periods as the dose of the drug was increased.

TABLE II. SUMMARY OF OBJECTIVE FINDINGS

DOSE (MG.)	NUMBER OF PATIENTS	BLOOD PRESSURE		PULSE	E.C.G. CHANGES
		SYSTOLIC	DIASTOLIC		
50	10	+ 8 mm.	+ 8 mm.	No change	No change
75	10	+ 8 mm.	+ 8 mm.	No change	No change
100	10	+15 mm.	+10 mm.	No change	Change in 7 (1)
200	10	+28 mm.	+15 mm.	+20	Change in 6 (2)
300	10	+40 mm.	+28 mm.	+25	Change in 8 (3)

Summary of ECG changes

(1) T_2 reduced one case (.2 mm); T_4 increased two cases (average, .2 mm); decreased in seven cases (average, .3 mm); ST_2 depressed in one case (.15 mm.).

(2) T_1 increased in one case (.2 mm.); decreased in three cases (average, .3 mm.); T_2 increased in one case (.2 mm.); decreased in three cases (average, .3 mm.); T_3 decreased in five cases (average, .4 mm.); T_4 decreased in six cases (average, .4 mm.); ST_2 depressed in one case (.2 mm.).

(3) T_2 decreased in four cases (average, .2 mm.); T_3 reduced in eight cases (average, .5 mm..); T_4 reduced in eight cases (average, .5 mm.).

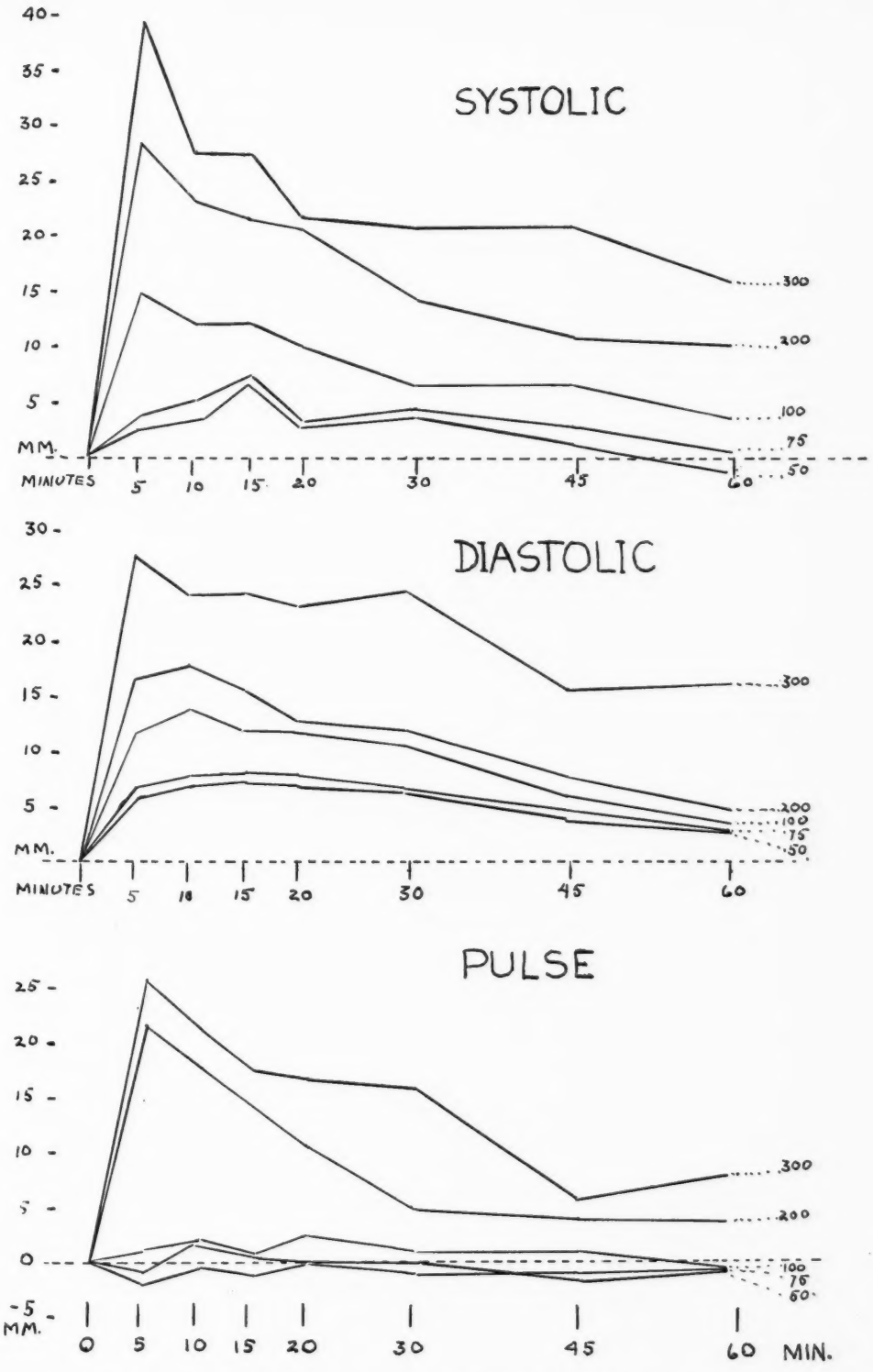

Fig. 2.—This graph shows the elevation of systolic and diastolic pressures expressed in millimeters of mercury on the upright scale and duration in minutes on the horizontal line. Increase in pulse rate is indicated on the upright scale as beats per minute.

EFFECT ON ELECTROCARDIOGRAMS

Alterations were chiefly increase in heart rate, increase or decrease in amplitude of QRS, T, and P waves. Slight depressions of S-T segments were noticed in one instance each, after 100 and 200 mg. P-R interval was prolonged in one case after 300 mg.; this patient had chorea several years ago.

Controls receiving distilled water only, showed no significant changes.

The marked cardiac acceleration, shortened diastole, evidence of auricular tachycardia, and changes in T waves and P waves indicated that Benadry solution, given intravenously, alters cardiac physiology and that the site of action is possibly myocardial.[5]

SUMMARY

1. Fifty patients were injected intravenously with Benadryl solution, with doses of 50, 75, 100, 200 and 300 mg.

2. Various systemic reactions were encountered, but none of sufficient severity to require treatment.

3. Normal saline solution should be used therapeutically to dilute the Benadryl solution.

4. Average systolic and diastolic blood pressures were elevated after all doses, particularly with 100, 200, and 300 milligrams. Although none of the patients in this series were hypertensive, the use of large intravenous doses of Benadryl is contraindicated in the presence of hypertension.

5. Electrocardiographic changes of sufficient significance occurred after 200 and 300 mg. of Benadryl solution, intravenously administered to preclude such doses in patients with heart disease.

The author wishes to thank Dr. Walter S. Wiggins for his assistance with the 50 and 75 mg. series and Mrs. Hazel Higgins for her technical skill with all the other electrocardiograms.

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STUDIES ON THE CHRONIC TOXICITY OF PYRANISAMINE MALEATE (NEO-ANTERGAN MALEATE) IN ANIMALS*

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THE pharmacologic properties and acute toxicity of N′-*p*-methoxybenzyl-N′, N′-dimethyl-N-*α*-pyridylethylenediamine maleate (Neo-Antergan maleate, a brand of pyranisamine maleate) have been described elsewhere.[1-3] Since this compound, as well as other antihistaminic agents, may be administered to patients over a prolonged period of time, it was considered desirable to investigate the effects of long term administration of Neo-Antergan to laboratory animals.

EXPERIMENTAL

I. *Small Doses in Rats.*—Neo-Antergan was administered for a period of approximately six months to male Carworth rats, beginning when the animals were one month of age. Group I (5 animals) received 10 mg. per kilogram by stomach tube five times weekly. For Group II (7 animals) the drug was mixed with the stock diet and fed *ad libitum*. The concentration of drug in the diet was 0.005 per cent in the beginning, and as this was well tolerated, the concentration was gradually increased until it was 0.01 per cent at the end. On the basis of food consumption data, it was estimated that approximately 15 mg. per kilogram of the drug were consumed daily during the latter part of the experiment. Group III (12 animals) served as untreated controls.

After six months, urine and blood specimens were collected and then the animals were sacrificed for pathologic study. Tissues were fixed in neutral 10 per cent formalin solution, sectioned, and stained with hematoxylin and eosin.

Good weight gains were shown by the animals of all groups during the experimental period. Table I shows that Neo-Antergan produced no significant deviation from normal in hematologic constituents. Quantitative determinations of constituents of pooled plasma or serum showed no deviation from normal in any group of animals. Constituents determined were as follows: Protein (range 5.9-6.1 Gm. per cent), fibrinogen (265-230 mg. per cent), cholesterol (58-68 mg. per cent), cholesterol ester: total ratio (0.86-0.93), phosphatase (8.2-10.5 units/100 c.c.), inorganic phosphate (3.1-3.2 mg. per cent P), chloride (100 milliequivalents/liter), glucose (98-111 mg. per cent), urea N (12.6-16.5 mg. per cent), creatinine (1.25-1.5 mg. per cent), creatine (5.7-7.6 mg. per cent), and plasma albumen: globulin ratio (0.72-0.90).

Urinary analyses revealed no differences among the three groups in volume, pH, blood, sugar, protein, or urobilinogen, nor were abnormalities seen upon microscopic examination of the urine. Neither gross nor microscopic changes attributable to the drug were found in the following tissues: hypophysis, thyroid gland, parathyroid gland, thymus, lung, heart, liver, spleen, pancreas, stomach, small and large intestine, adrenal gland, kidney, testes, seminal vesicles, prostate, and urinary bladder.

*From the Merck Institute for Therapeutic Research.

TABLE I. TERMINAL HEMATOLOGIC VALUES IN ANIMALS AFTER ADMINISTRATION OF NEO-ANTERGAN

	RATS, AVERAGE VALUES*			DOGS TREATED†				MONKEYS‡		
	GROUP I	GROUP II	GROUP III	NO. 867	NO. 868	NO. 869	CONTROL	NO. 137	NO. 146	NO. 139
R.B.C. (millions/mm.)	8.80	8.55	8.20	5.28	5.84	5.29	5.04	4.88	4.38	5.02
Hemoglobin (Gm. per cent)	15.6	15.7	14.9	11.45	13.2	11.6	10.9	12.1	11.7	12.7
Hematocrit (per cent)	50.9	49.0	48.2	42	49	42	40	45	44.5	48
W.B.C., total	11,200	13,688	13,507	13,000	10,280	10,800	10,680	7,680	7,520	10,480
W.B.C., differential:										
lymphocytes	80	82	75	26	28	28	29	68	53	66
polymorphonuclears	19	17	24	73	68	66	68	32	42	32
monocytes	0	0	0	0	0	0	1	0	0	1
eosinophiles	1	1	1	1	4	4	2	0	5	0
basophiles	0	0	0	0	0	2	0	0	0	1

*Rats of Groups I and II were treated for six months. Group III were untreated controls.

†Dogs Nos. 867, 868, and 869 were treated for six months.

‡Monkeys Nos. 137 and 146 received 50 mg./kg. daily, and No. 139, 100 mg./kg. daily, for thirty-five days.

II. *Large Doses in Rats.*—In order to determine, if possible, whether overdoses of Neo-Antergan might have a predilection for producing pathologic changes in any particular organ, several groups of rats were given daily doses by stomach tube. The groups and the doses they received daily were as follows:

Group A (5 animals) 50 mg. per kilogram for 32 days. Group B (5 animals) 100 mg. per kilogram for 32 days. Group C (5 animals) 200 mg. per kilogram for 32 days. Group D (5 animals) saline-dosed controls for Groups A, B, and C. Group E (20 animals) 500 mg. per kilogram for 61 days. Group F (12 animals) untreated controls for Group E. Group G (18 animals) 1000 mg. per kilogram for 42 days. Group H (5 animals) untreated controls for Group G.

No toxic signs were observed in the animals of Groups A, B, and C. They gained weight at the same rate as their controls. Hematologic studies made at intervals of five to ten days in Group C revealed no abnormalities. The two larger doses, however, proved to be toxic. Of the twenty rats in Group E, ten died and four were sacrificed during the course of the experiments. Of the eighteen rats in Group G, two died after a single dose, eight died after ten to thirty-eight doses, two rats were sacrificed after fourteen doses, and the remaining six rats survived.

The toxic sign most frequently noted in the animals receiving the two largest doses was excessive salivation. Mild convulsions were seen in some of the animals, especially those which did not survive the entire course of treatment. In general, these toxic signs were of short duration and the animals continued to exhibit good weight gains up to within a day or two of death. However, at this time, the animals often appeared lethargic and seemed cold to the touch. The average daily weight gains for those surviving the entire experiment were: Group E, 2.6 grams; Group F, 3.1 grams; Group G, 2.7 grams; Group H, 3.1 grams. Thus, even extremely large doses given once daily had very little retarding effect on growth in those animals which did not succumb to the acute toxic effect.

Although the two highest doses were definitely at a toxic level, as shown by the failure of many of the rats to survive, autopsy revealed no evidence, either gross or microscopic, that there was any specific damage to any particular organ or tissue. The only positive finding was a slightly higher kidney-body weight ratio in Groups E and G than in their controls. The tissues studied are enumerated in Section I.

III. *Experiments on Dogs.*—A litter of seven beagle pups was divided into two groups. Neo-Antergan, 20 mg. per kilogram in gelatin capsules, was administered five times weekly to one group of two males and two females, while the second group, two females and one male, served as untreated controls. The pups were fifty-five days old when treatment started. One experimental animal and two controls were observed for four months, while observations were continued for six months on the others. No difference was noted in the growth curves of experimental and control animals.

Hematologic determinations were made at monthly intervals. Final values for the four dogs observed during the entire six months are shown in Table I.

At no time was there any evidence that the drug produced hematologic variations. Prothrombin levels remained normal in all dogs throughout the experimental period.

Blood and urine specimens were also obtained at intervals for biochemical studies. Plasma constituents were not affected by the drug after six months of treatment. The same constituents were determined as enumerated (Section I) for the rats. The urine showed no significant differences between experimental and control animals in volume, pH, blood, sugar, protein, or urobilinogen. The dogs were sacrificed for study at the end of the experiment. In no instance was there any evidence, either gross or microscopic, of tissue injury produced by Neo-Antergan.

IV. *Experiments on Monkeys.*—Neo-Antergan was administered by stomach tube to four mature rhesus monkeys. Two of the animals received 50 mg. per kilogram in single dose daily and two were given 100 mg. per kilogram once daily. Three of the animals tolerated the drug quite well and appeared healthy throughout, exhibiting no toxic signs at any time, although the dosing was continued for thirty-five days. In the fourth monkey, 100 mg. per kilogram proved to be a toxic dose. Four and one-half hours after the fifth dose, marked tremors appeared and there was a small amount of vomitus. The animal soon became comatose. Corneal reflex was absent. The animal was sacrificed for pathologic study, and there were no gross findings except generalized congestion of the viscera. Histologic examination on this monkey, as well as the others, revealed no lesions which could be attributed to the drug, except congestion in the animal as noted.

Hematologic determinations were made at approximately weekly intervals. Table I shows the values at the end of the experiment. It is evident that all values obtained were within normal limits for the monkey. Urinalysis also revealed no abnormalities in these animals.

The results on monkeys, as well as on the other animals, show that very large amounts of Neo-Antergan can be given with safety when the drug is administered in divided doses over a long period of time. Thus, one monkey was apparently unaffected by an amount of Neo-Antergan totaling 3,500 mg. per kilogram and two others, by a total of 1,750 mg. per kilogram each. The higher daily doses must have been near the toxic level, since one monkey did succumb after five doses of 100 mg. per kilogram each. Dogs developed no signs of toxicity after receiving 2,600 mg. per kilogram over a six-month period, and several rats maintained nearly normal growth although they received a total dose of 42,000 mg. per kilogram over a forty-two day period. From these results, it seems unlikely that Neo-Antergan in small or moderate doses has a cumulative effect.

SUMMARY

1. Neo-Antergan maleate (brand of pyranisamine maleate) has been administered to rats, dogs, and monkeys for varying lengths of time up to six months. The following doses appeared to be entirely safe: (a) In rats, 10 mg. per kilogram five times weekly for six months and up to 200 mg. per kilogram daily

for thirty-two days; (b) in dogs, 20 mg. per kilogram five times weekly for six months; (c) in monkeys, 50 mg. per kilogram daily for thirty-five days. No toxic signs, nor any hematologic, biochemical, or pathologic abnormalities were found in the animals on these doses.

2. One monkey tolerated 100 mg. per kilogram daily for thirty-five days, but this proved to be a toxic level for another monkey which succumbed after five such doses. In rats, daily doses of 500 mg. per kilogram for sixty-one days and 1,000 mg. per kilogram for forty-two days proved to be toxic for some animals because many died on these dose levels. Those which survived, however, grew at a nearly normal rate.

3. There is no evidence that Neo-Antergan has a cumulative effect at small or moderate doses, since the drug may be administered over a long period of time with no apparent ill effects.

The authors are indebted to Mr. John F. Flanagan for quantitative determinations of serum and plasma constituents and for urinalyses.

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USE OF ANTIHISTAMINIC DRUGS IN TREATING PATIENTS ALLERGIC TO LIVER EXTRACT*

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IN CERTAIN diseases it is necessary to administer by the parenteral method preparations extracted from liver. This is true in pernicious anemia and in other conditions presenting macrocytic anemia, such as the sprue syndrome. Because manifestations of allergy develop in a small number of patients after the use of preparations which contain liver, it has become necessary to devise methods of administration which will enable such individuals to tolerate therapeutic doses of liver extract.

Although there are relatively few published reports of cases in which reactions of hypersensitivity to liver extract have occurred, nevertheless, such reactions are fairly common. To date, only somewhat more than fifty case reports on this subject are to be found in the literature.[1] It is our wish to review facts concerning this therapeutic problem and to outline a method which has proved successful in meeting it.

The incidence of hypersensitivity to liver extracts administered parenterally is not limited to patients who present other evidences of atopy or give a familial history of it. Harten and Walzer[2] in 1940, on reviewing the histories of twenty-eight patients exhibiting hypersensitivity to liver extract, found that only seven gave histories indicative of previous allergic disease.

Some reactions to concentrated extracts of liver have been caused by a histamine-like substance in certain batches of liver extract.[2] In some patients manifestations of hypersensitivity undoubtedly belong in this group. Also reactions may follow a chance intravenous injection of liver extract with an injection meant to be given intramuscularly. The precaution of withdrawing the plunger of the syringe should obviate the likelihood of this taking place.

Concerning those cases in which true hypersensitivity obtains, certain facts are known. The substance causing a reaction appears to be intimately connected with the antianemic principle.[3] This is especially evident in patients in whom reactions occur only with doses of liver extract beyond a certain antianemic titer. The severity of the reaction is related to the number of units of antianemic activity rather than to the bulk of the substrate derived from liver. Feinberg, Alt, and Young[3] have shown that the antigen is "not species specific nor strictly organ specific but it is specific to a special organ fraction, bound up with the antianemic fraction"; that is, it causes the development of antibodies specific to the antianemic fraction of liver substance regardless of the animal from which the gland is taken.

Although it may occasionally be true that different methods of preparation will affect the ability of a liver extract to precipitate reactions of hypersensitivity, in general this is not true. This is not surprising when the relationship

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between the offending substance and the antianemic principle is considered. Feinberg and co-workers in 1943 showed also that certain extracts of liver may retain their ability to elicit reactions in hypersensitive individuals although they will give negative chemical tests for protein and carbohydrate. It is not clear where between the boundaries of atopy and anaphylaxis this problem of hypersensitivity to liver extract belongs. The lack of protein in the offending substance is contrary to favored theories concerning the mechanism of allergy unless protein of the body should secondarily become involved in the reaction, as is probable in the case of drug allergies.[4] Suggesting an anaphylactic type of mechanism is the virtual lack of reactions until after a prolonged period of treatment with liver extract. Anaphylactic reactions differ characteristically from atopic reactions in the formation of precipitins.[5] Several observers have demonstrated precipitins in the serum of patients hypersensitive to liver extract.[6, 7] Such findings have by no means been constant, for others have failed to demonstrate their presence.[1] Why reactions may occasionally occur in subjects who usually tolerate liver extract without difficulty is still unanswered. Perhaps the chance intravenous administration or the use of histamine-contaminated extracts may account for some such instances.

Opinion remains divided as to the value of skin testing in determining whether or not patients will exhibit reactions following the parenteral use of liver extract. Allin and Meyer[8] in 1940 concluded that such tests were of questionable value after finding that eleven of fourteen normal subjects gave positive skin reactions to high dilutions of the extract tested intracutaneously. Kaufman, Farmer, and Reich[1] in 1943 found that normal subjects would frequently give a positive skin test with wheal formation up to 15 mm. in diameter following an intracutaneous injection of liver extract. Only larger reactions or reactions with pseudopods were considered by them to be of significance. Others apparently have attributed greater significance to skin tests for sensitivity to liver extract.[9]

The checking of the cutaneous sensitivity of patients to liver extract before treatment with the extract is started seems impractical because of the infrequency with which systemic reactions to parenterally administered liver extracts occur and because of the high incidence of cutaneous sensitivity in individuals who exhibit no allergic manifestations, as mentioned previously. Likewise, such generalized reactions almost invariably occur only after prolonged administration of liver extract. With only a positive reaction to a skin test as evidence of hypersensitivity to liver extract, one would hesitate to abandon or delay the use of a substance so urgently needed as liver is in cases of pernicious anemia. Determining the degree of cutaneous reactivity of patients known to be sensitive to liver extract is of value in an academic sense only inasmuch as greater understanding of this problem will be achieved in part through such studies. In every instance even though reactions do occur, it is essential that treatment in some form be resumed because of the serious nature of the disease for which liver extract is being given. For these reasons we have not routinely checked the cutaneous reactions of the patients to the various preparations of liver.

CASES STUDIED

In the years 1935 through 1944 approximately 1,900 patients with macrocytic anemia were studied at the Mayo Clinic. The great majority of these patients had pernicious anemia. Patients who had sprue, liver disease, and malignant lesions of the gastrointestinal tract were likewise represented in smaller numbers. A review of these cases disclosed twelve instances in which a bona fide allergic reaction had occurred after treatment with liver extract. Data on eight additional patients observed since 1945 form the basis for this report concerning a method of therapy. Instances in which the correlation between the use of liver extract and the reaction was not clear or in which an atypical manifestation of hypersensitivity was elicited were excluded from consideration.

Of the twenty patients considered to have had a reaction to liver extract, ten were men and ten were women. They varied in age from 18 to 81 years. Of these patients nineteen had pernicious anemia, while one, a youth aged 18 years, had macrocytic anemia, the nature of which was not determined at the time he was under observation. The duration of parenteral treatment with liver extract before the first manifestation of hypersensitivity appeared varied widely. One patient first noted a reaction after the fourth injection, another after twelve years of treatment.

The twenty patients studied had several different forms of allergic reactions after the use of liver extract parenterally. Most commonly observed was urticaria or angioneurotic edema, or both. Fourteen patients had this type of reaction. The second most frequently seen reaction was an anaphylactic shock-like reaction which developed in six subjects. In these twenty patients atopic dermatitis was seen twice and diarrhea occurred once after oral administration of liver extract.

From a review of the case records, some of which date from the early years of treatment with liver extract, some pertinent data were unobtainable. In Tables I and II the nature of the reactions and the disposition of the cases are presented.

In cases of pernicious anemia parenteral administration of liver extract is the method of choice, particularly when the erythrocyte count and concentration of hemoglobin are low, when oral administration is inadequately sustaining the patient's hemopoietic function, or when manifestations of degeneration of the central nervous system are present. Because of the seeming failure of folic acid to control the neurologic lesions associated with pernicious anemia[10] we felt it imperative to devise a program of treatment employing liver extract that could be tolerated by patients who previously had exhibited allergic reactions after its use.

TREATMENT OF REACTIONS

The recent introduction of drugs such as diphenhydramine hydrochloride (Benadryl), tripelennamine hydrochloride (Pyribenzamine hydrochloride), and N-p-methoxybenzyl-N-dimethylaminoethyl α-aminopyridine (Neo-Antergan) has made available to the medical profession antihistaminic preparations of great

TABLE I. CASES IN WHICH REACTIONS TO LIVER EXTRACT OCCURRED PRIOR TO INTRODUCTION OF ANTIHISTAMINIC DRUGS*

CASE	AGE	SEX	DURATION OF TREATMENT BEFORE REACTION	REACTION		PERSONAL HISTORY OF ALLERGY†	RESULTS
				TYPE	TREATMENT		
1	18	M	3½ mo.	Severe asthma shortly after injection	Changed to concentrated liver extract (Lederle) by intramuscular route	Asthma	Mild asthma at 1 subsequent (third) injection; no trouble on reduced dose
2	55	F	2 yr.	Anaphylactic shocklike syndrome with loss of consciousness (3 times)	Changed to a liver extract for oral use	Negative	Outcome unknown; tolerating oral doses liver extract when dismissed
3	81	F	10 yr.	Repeated urticaria following injection of liver extract of unknown type	Small amounts of epinephrine were given simultaneously with liver extract	Negative	Treatment tolerated at time of last communication
4	78	M	11 yr.	Anaphylactic shocklike syndrome with loss of consciousness (2 times)	Desensitization with increasing doses of liver extract; histaminase	Negative	Treatment tolerated at time of last communication
5	32	F	3 yr.	Repeated urticaria following injections	Changed to a liver extract for oral use	Vasomotor rhinitis; asthma	Treatment tolerated at time of last communication, 5 years after change of medication
6	43	F	12 yr.	Urticaria and angioneurotic edema	Desensitization with concentrated liver extract (Lederle)	Negative	Outcome unknown
7	51	M	1 yr.	Angioneurotic edema; laryngeal edema	Desensitization with concentrated liver extract (Lederle)	Negative	Rapid desensitization uneventful; tolerating treatment at time of last communication 1 month after desensitization
8	60	M	2 yr.	Repeated urticaria following injections	Changed to a liver extract for oral use	Negative	Treatment tolerated at time of last communication
9	78	M	1 yr.	Anaphylactic shocklike syndrome after 4 consecutive injections	Changed to a liver extract for oral use	Negative	Unknown
10	48	F	4 yr.	Urticaria and angioneurotic edema	Desensitization with increasing doses of liver extract; histaminase	Negative	Only 2 minor similar reactions in following period of 5 years
11	43	F	16 mo.	Urticaria and angioneurotic edema (3 times)	Desensitization with increasing doses of liver extract; histaminase	Negative	Treatment tolerated at time of last communication, 3 months after desensitization
12	78	M	8 yr.	Anaphylactic shocklike syndrome following injections of liver extract (9 times)	Desensitization with concentrated liver extract; histaminase	Negative	Treatment tolerated at time of last communication, 4 years after desensitization

*The clinical diagnosis in all cases except Case 1 was pernicious anemia; in Case 1 it was macrocytic anemia of unknown type.
†Family history of asthma in Cases 1 and 10; in other cases no family history of allergy.

TABLE II. SENSITIVITY TO LIVER EXTRACT TREATED BY DESENSITIZATION WITH CONCENTRATED LIVER EXTRACT (LEDERLE) COMBINED WITH ADMINISTRATION OF ANTIHISTAMINIC DRUGS AS INDICATED IN TABLE III: RESULTS IN EIGHT CASES*

CASE	AGE	SEX	DURATION OF TREATMENT BEFORE REACTION	REACTION (TYPE)	PERSONAL HISTORY OF ALLERGY†	RESULTS OF TREATMENT OF REACTION
13	49	F	3 yr.	Repeated episodes of urticaria and flushing after intramuscular injections; diarrhea after oral use of liver extract	Negative	Tolerated liver extract desensitization program; gradually discontinued use of Benadryl because of increasing drowsiness; had no allergic reactions at time of last communication 8 months after desensitization
14	63	F	1 yr.	Loss of consciousness following injection on "several" occasions; atopic dermatitis after both oral and intramuscular use of extracts‡	Dermatitis medicamentosa with "sulfa" drugs	Tolerated liver extract "desensitization"; had no difficulty at time of last communication, 19 months after program of desensitization
15	48	M	5 yr.	Repeated episodes of urticaria following injections of liver extract	Negative	Developed Addison's disease at approximately the time his sensitivity to liver extract began (see discussion for remarks concerning the significance of this coincidental development of disease); occasional mild urticaria in desensitization inadequately controlled with Benadryl; oral therapy with liver extract started 1 year after desensitization
16	37	M	Fourth injection	Angioneurotic edema repeatedly following injection of liver extract	Negative	Developed anaphylactic shocklike syndrome in the course of desensitization, following 0.5 c.c. undiluted concentrated Lederle's liver extract; subsequently tolerated this quantity of extract given intramuscularly; tolerating treatment at time of last communication one month after desensitization
17	67	M	2 yr.	Repeated episodes of generalized urticaria following intramuscular injection	Negative	Tolerated liver extract intramuscularly having no difficulty at time of last communication, 6 months after desensitization; discontinued use of Benadryl after two months
18	68	F	4 yr.	Repeated episodes of angioneurotic edema following intramuscular injection	Negative	Tolerated liver extract intramuscularly having no difficulty at time of last communication, 8 months after desensitization
19	66	F	1 yr.	Atopic dermatitis, repeated episodes of urticaria and angioneurotic edema	Asthma; atopic dermatitis	Failure of Benadryl; able to tolerate 0.5 c.c. doses of liver extract twice weekly after desensitization and use of Pyribenzamine but has slight urticarial reactions
20	41	F	6 yr.	Repeated episodes of angioneurotic edema and urticaria following intramuscular injections	Negative	Tolerated desensitization without incident

*Clinical diagnosis in all cases was pernicious anemia. In Case 15 the patient also had Addison's disease.

†Family history of urticaria in Case 14; in other cases no family history of allergy.

‡Details of treatment are given in Table III.

therapeutic value.[9] Particularly is this true in the treatment of urticaria and angioneurotic edema, common manifestations of hypersensitivity to liver extract. It has appeared, therefore, that these drugs might prove helpful in the treatment of patients requiring treatment with liver preparations to which they had become sensitized. Accordingly, we have added to our previously employed program of desensitization the use of an antihistaminic drug. Benadryl, a drug with which considerable experience has been obtained, was selected.

While the effect of Benadryl is apparently not cumulative, the usual duration of action being only five to eight hours, we have added the precaution of administering it forty-eight hours prior to an attempt to desensitize a patient. As experience is accumulating, such a practice is proving to be of doubtful necessity. Throughout the period of rapid desensitization the antihistaminic drug is used continuously. As injections of liver extract are given at increasingly greater intervals, the antihistaminic drug is given on the day prior to, and on the day of, the injection of the liver extract. Ultimately, medication is used only on the day liver extract is to be administered. It is then a good practice to employ a somewhat greater dose of Benadryl. We have used from 150 to 200 mg. of it daily in three or four divided doses.

In administering the concentrated liver extract, certain principles should be observed. The initial dose should be of a high dilution. Subsequent doses of liver extract may be increased progressively in size and may be given at short intervals until a substantial amount having an effective therapeutic value is administered. Thereafter, the liver extract should be injected at progressively longer intervals, given at first daily, then every second day, then twice a week, and finally once a week in doses adequate to maintain pernicious anemia in a state of remission. At no time should the interval between injections of liver concentrate be greater than one week. A return of sensitivity frequently follows a prolonged lapse of treatment. It is a good practice to hospitalize the patient for approximately twenty-four hours during the time rapid desensitization to liver extract is undertaken. Close observation of the patient for reactions and prompt treatment of any untoward symptoms are thereby assured. The method we have employed is presented in Table III.

Should allergic reaction to liver extract occur, it may be necessary to administer epinephrine. A delay in the rate of absorption of the liver extract may be obtained by applying a tourniquet to the extremity into which the injection was made. This tourniquet may be released for periods of increasing length. Minor reactions consequent to an injection of liver extract do not warrant discontinuance of the program of desensitization. However, after a reaction the next attempt at desensitization should begin with a smaller dose. This dose should be no greater than one-half the previously tolerated dose. It would appear that greater doses of Benadryl or the use of another antihistaminic drug better tolerated in large doses should be employed when a reaction to liver extract has been encountered while this method of desensitization is being employed.

On eight occasions we have had opportunity to employ this method. The essential facts from these case histories are summarized in Table II.

TABLE III. DESENSITIZATION TO LIVER EXTRACT

First day	50 mg. of Benadryl by mouth three times a day after meals
Second day	50 mg. of Benadryl by mouth three times a day after meals
Third day	(Epinephrine and syringe should be made available)
8:00 A.M.	100 mg. of Benadryl by mouth
9:00 A.M.	0.1 c.c. of 1:100 dilution of concentrated liver extract injected subcutaneously
9:30 A.M.	0.2 c.c. of 1:100 dilution of concentrated liver extract injected subcutaneously
10:00 A.M.	0.4 c.c. of 1:100 dilution of concentrated liver extract injected subcutaneously
10:30 A.M.	0.7 c.c. of 1:100 dilution of concentrated liver extract injected subcutaneously
11:00 A.M.	0.1 c.c. of 1:10 dilution of concentrated liver extract injected intramuscularly
11:30 A.M.	0.2 c.c. of 1:10 dilution of concentrated liver extract injected intramuscularly
12:00 M.	0.4 c.c. of 1:10 dilution of concentrated liver extract injected intramuscularly; 50 mg. of Benadryl by mouth
12:30 P.M.	0.7 c.c. of 1:10 dilution of concentrated liver extract injected intramuscularly
1:00 P.M.	0.1 c.c. of undiluted concentrated liver extract injected intramuscularly
1:30 P.M.	0.15 c.c. of undiluted concentrated liver extract injected intramuscularly
2:00 P.M.	0.25 c.c. of undiluted concentrated liver extract injected intramuscularly
2:30 P.M.	0.4 c.c. of undiluted concentrated liver extract injected intramuscularly
3:00 P.M.	0.5 c.c. of undiluted concentrated liver extract injected intramuscularly
6:00 P.M.	50 mg. of Benadryl by mouth
Fourth day	50 mg. of Benadryl by mouth three times a day after meals; 0.5 c.c. of undiluted concentrated liver extract injected intramuscularly one hour following first dose of Benadryl
Fifth day	Same as on fourth day
Sixth day	50 mg. of Benadryl by mouth three times a day after meals
Seventh day	Same as on fourth day
Eighth day	50 mg. of Benadryl by mouth three times a day after meals
Ninth day	Same as on fourth day
Tenth day	50 mg. of Benadryl by mouth three times a day after meals
Eleventh day	50 mg. of Benadryl by mouth three times a day after meals
Twelfth day	Same as on fourth day
Fourteenth day	50 mg. of Benadryl by mouth three times a day after meals
Fifteenth day	Same as on fourth day
Seventeenth day	50 mg. of Benadryl by mouth three times a day after meals
Eighteenth day	Same as on fourth day; thereafter weekly as on fourth day; use of Benadryl on the day preceding the injection of liver extract is eliminated

COMMENT AND SUMMARY

It is occasionally necessary to administer extracts of liver to patients sensitive to this substance. The essential features in twenty cases in which allergic reactions resulted from the parenteral use of concentrated liver extract were studied. In eight recent cases the combined use of antihistaminic drugs and liver extracts has proved helpful in the solution of this problem. In only two of these patients have untoward reactions necessitated the stopping of parenteral administration of liver extract. One was a patient whose allergic manifestation was that of atopic dermatitis (Case 19). Pyribenzamine is being successfully used in a similar program.

The other patient (Case 15) was of particular interest. This patient tolerated injections of liver for five years and became sensitive coincidently

with early manifestations of Addison's disease. Sensitivity to histamine has been definitely shown to be affected by the adrenal cortical function.[11-13] Adrenalectomy or hypophysectomy, allowing adrenal cortical atrophy, in guinea pigs or in rats will greatly decrease the minimal lethal dose of histamine for those animals. Replacement therapy by extracts of adrenal cortex will allow the natural resistance to histamine, which in the rat is high, to assume essentially normal values.[13] With these facts in mind it is apparent that the development of Addison's disease may have contributed to the sensitivity the patient manifested to the injection of liver extract. Bringing the Addison's disease under control likewise may have contributed to his improved tolerance to extracts of liver subsequently administered.

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SIDE EFFECTS OF THREE ANTIHISTAMINIC DRUGS

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MANY reports of various side effects of diphenhydramine hydrochloride (Benadryl) and tripelennamine hydrochloride (Pyribenzamine) have been published.[1-9] Usually these side effects consisted of drowsiness, dizziness, or nervousness, but more severe reactions such as "Benadryl jag,"[2] unconsciousness,[5] narcolepsy,[6] and epileptiform movements[9] have been seen. Such reactions are commonly reported to appear soon after beginning the administration of the drug and later to become less marked. From clinical evidence alone, Pyribenzamine is said to cause fewer side effects than Benadryl.[7] Recently, a combination of 25 mg. diphenhydramine hydrochloride and 100 mg. aminophylline (per tablet), Hydryllin, has been added to the antihistaminic drugs. The present study was made to obtain a more adequate basis for the comparison of the side effects caused by these three drugs.

METHOD

The drugs were administered to a series of ten healthy college students. Five experiments were performed on each subject, one each with Benadryl, Pyribenzamine, and Hydryllin, and two with lactose as a control. The subjects were not aware of the identity of the drug being used in any specific experiment. The drugs were administered with food in the therapeutic dose of 50 mg. Benadryl, 50 mg. Pyribenzamine, or 125 mg. Hydryllin at 7:00 A.M., 11:00 A.M., and 3:00 P.M. The tests were done at 3:30 P.M. except in two cases in which the reaction after the first dose was so severe as to necessitate discontinuance of the experiment. In these instances no more drug was given and testing was done at 10:00 A.M.

The following tests and observations were carried out:

1. *Mental Ability Test:* This letter cancellation test, originally proposed by Bourdon,[10] measures the mental capabilities of the subject in performing a specific operation, the cancellation with three marks (circle, cross, and dash), during a period of four minutes, of three designated letters as they appear in a chosen printed text. The results are expressed as the average of the per cent error in marking the text and the per cent material covered under the influence of the drug as compared to the normal ability after taking lactose.

2. *Reaction Time‡:* The apparatus used for this test of speed of performance consists of two boards, one for the operator and one for the subject, a sound-

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‡This test is being used by the Child Research Council (The Department for the Study of Human Growth) of the University of Colorado Medical Center. While it has been in use for several years, it has not been previously described in the literature.

proof timer,* and associated electrical circuits. The circuit diagram is shown in Fig. 1. At a signal given by the operator the subject closes the key. When the light appears as a result of the operator's closing his key, the subject opens his. The interval during which the lamp is lighted is measured by the timer in 1/120 sec. and is recorded as the reaction time. The interval after the ready signal should be about two seconds[11] but a slight variation of one to three seconds is required to prevent anticipation of the signal by the subject. Three practice trials and five test trials were performed. If the practice trials showed a similar average and variation to the test trials the latter were used; otherwise another series of trials was done. The results are expressed as reaction time in 1/120 second.

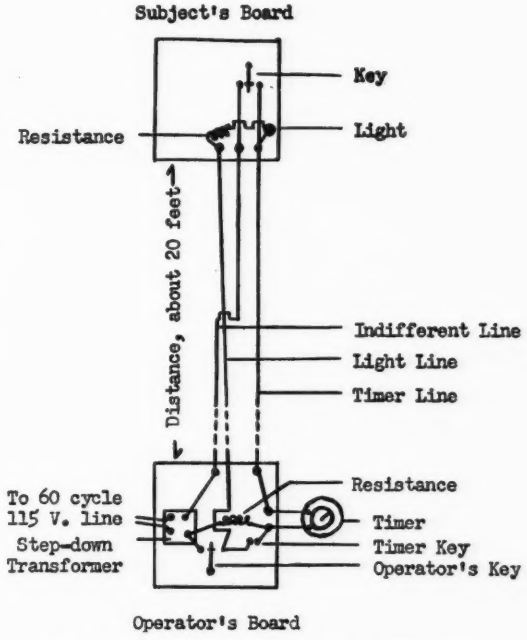

Fig. 1.—Diagram of reaction time apparatus.

3. *Two-Point Discrimination*[12]*:* This test of sensory perception was performed in the usual manner with calipers and a sufficient number of trials to give consistent results. The results are expressed as the minimum distance in centimeters at which two points could be distinguished on the volar surface of the forearm.

4. *Blood Pressure, Pulse, and Respiration:* Observations were made with the subjects in a sitting position after a five minute rest period.

5. *Signs and Symptoms:* Noticeable objective and subjective changes in the subjects were recorded.

*The timer is an impulse counter manufactured by the Central Scientific Company, Chicago, Ill.

RESULTS

The results obtained are shown in Figs. 2, 3, and 4, which compare experimental results with lactose controls. The data are summarized in qualitative form in Table I in which changes tending to interfere with the individual's ability to respond to his environment are indicated by minus signs (worsened mental score, increased reaction time, increased two point discrimination distance), no change by n. c., and improved reactions by plus signs. The total is also recorded for comparison between the three drugs.

TABLE I. SIDE EFFECTS OF ANTIHISTAMINIC DRUGS

TEST	PYRIBENZAMINE		BENADRYL		HYDRYLLIN	
	NO. SUBJECTS	RESPONSE	NO. SUBJECTS	RESPONSE	NO. SUBJECTS	RESPONSE
Bourdon test	3	+	5	+	6	+
	3	n. c.	1	n. c.	1	n. c.
	4	–	4	–	3	–
Reaction time	1	+	4	+	6	+
	4	n. c.	3	n. c.	1	n. c.
	5	–	3	–	3	–
Two-point discrimination	2	+	3	+	4	+
	2	n. c.	3	n. c.	1	n. c.
	6	–	4	–	5	–
Totals	6	+	12	+	16	+
	9	n. c.	7	n. c.	3	n. c.
	15	–	11	–	11	–

+, Increased response to external stimuli.
–, Decreased response to external stimuli.
n. c., No appreciable change in response to external stimuli.

The pulse, respiratory rate, and blood pressure showed no consistent change but there was a tendency for Benadryl to lower both systolic and diastolic blood pressure (six subjects) and to reduce the respiratory rate (seven subjects). Hydryllin showed a similar effect on the blood pressure. The effect was especially noticeable in one subject who received only 50 mg. of Benadryl and became very drowsy. It was necessary to put this subject to bed for two hours before she could resume her customary work. She complained of dizziness, headache, and drowsiness. However, she did not lose consciousness or truly sleep, but remained in a partial hypnotic state.

After the first Benadryl capsule, two other subjects showed an especially noticeable reaction which seemed to subside with further dosage. Both subjects were working in a chemistry laboratory where they found it impossible to dilute solutions accurately to volume. The defect was not in that they failed to recognize the motor response required but rather in that they found it impossible to stop the flow into the flask at the desired level. The difficulty was noticed by the instructor in charge who did not know that the students were under the influence of a drug. Such reactions were not observed with either Pyribenzamine or Hydryllin.

DISCUSSION

Examination of the figures indicates that, in general, there was no consistent effect obtained from any of the three drugs tested. However, it appears that while Pyribenzamine decreases the efficiency of a greater number of

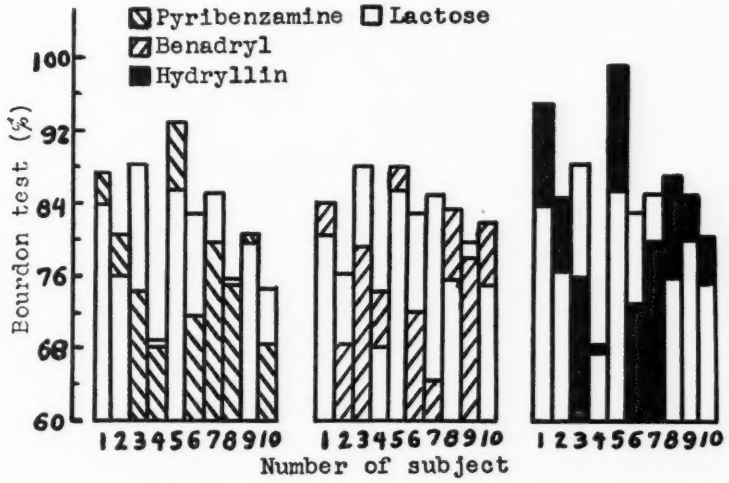

Fig. 2.—Percentage score of Bourden test in ten subjects.

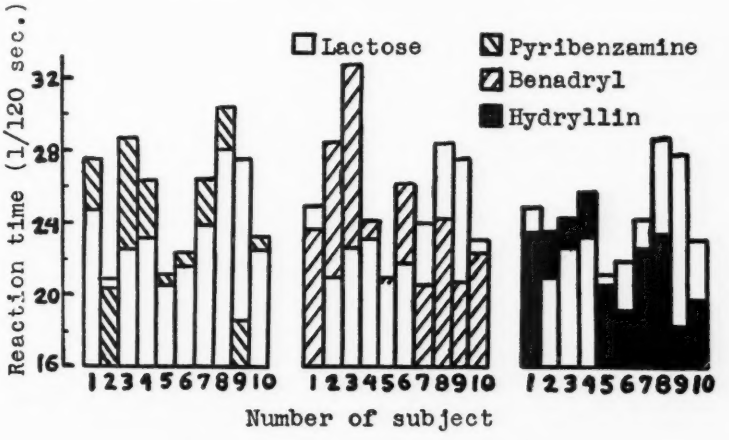

Fig. 3.—Reaction time in ten subjects.

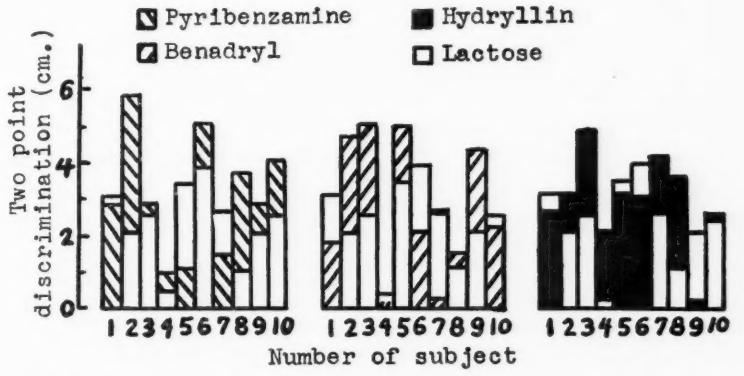

Fig. 4.—Minimum distance of two-point discrimination in ten subjects.

individuals than does Benadryl, the latter sometimes causes a more marked reduction in response to external stimuli. This is also evidenced by the fact that three individuals (whose reactions have been described) were very seriously affected both subjectively and objectively by Benadryl, while none were so affected by Pyribenzamine or Hydryllin. The wide variation in the results makes comparisons difficult but some conclusions can be drawn from Table I. It is shown that a heightened response was brought about by Benadryl in twelve, by Pyribenzamine in six, and by Hydryllin in sixteen tests; Benadryl caused a decreased response in eleven, Pyribenzamine in fifteen, and Hydryllin in eleven tests. It may be seen from these results that Pyribenzamine caused the greatest number of depressant effects and Hydryllin the largest number of improvements in those factors tested which are utilized by an individual in responding to stresses in the environment, such as making quick decisions and acting rapidly in conditions of physical emergency. All three drugs caused a decreased efficiency in some individuals as revealed by one or more of the tests.

Since some subjects show an adverse reaction with any of these drugs, care should be taken to observe carefully a patient who is first given one of them, especially Benadryl, and to warn the patient of the dangers inherent in his reduced ability to react quickly. These factors are especially important in the common occupation of driving an automobile where a fraction of a second difference in reaction time may mean the difference between a serious accident and safety.

SUMMARY

1. A comparison of Benadryl, Pyribenzamine, and Hydryllin was made on the basis of their effect in therapeutic dosage on mental ability, reaction time, two point discrimination distance, pulse rate, blood pressure, and respiratory rate.

2. Mental ability, reaction time, and minimum distance of two point discrimination were appreciably altered by these drugs in over one-half the subjects tested.

3. Pyribenzamine caused a greater number of individuals to show a decrease in efficiency than did Benadryl, but the latter occasionally caused decreases of considerably greater magnitude.

4. Hydryllin caused an increased efficiency in a majority of the subjects but adversely affected a few.

5. It is suggested that patients begun on therapy with these antihistaminic drugs be at first kept under strict observation.

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FATALITY ASSOCIATED WITH BENADRYL THERAPY*

Report of a case

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SINCE Benadryl (beta-dimethylamino-ethyl benzhydryl ether hydrochloride) has become a popular drug with the medical profession, many reports on its use in allergic diseases have been published. Almost all of these have been discussed and emphasized the distressing side effects which frequently occur and which in some cases call for discontinuance of the drug. However, there has not previously been published any case in which the administration of Benadryl has been associated with a fatality. Such is the purpose of this paper.

CASE REPORT

A 47-year-old wife of a soldier was admitted to the AAF Station Hospital, Fort George Wright, Washington on June 11, 1947 with a chief complaint of difficulty in breathing.

The patient gave a history of intermittent attacks of bronchial asthma of ten years' duration. She had been treated in the past with "shots" which relieved the acute attacks and also had taken several types of pills, the contents of which were unknown to the patient. The attacks were severe and recurrent, the last occurring in October, 1946. Between attacks, the patient felt well and breathed without difficulty. There was no history of precordial pain or dyspnea on exertion. During attacks, she had soreness throughout her chest and abdomen from coughing but had had no other chest pain. She had noted moderate swelling of the ankles in the evenings for many years.

Physical examination on admission revealed an apprehensive, but lethargic, white female of 47 years, appearing her stated age. She was severely dyspneic and had paroxysms of cough with facial hyperemia. The cardiac rhythm was regular and the heart sounds were normal; no murmurs were heard. Wheezing with inspiratory and expiratory râles was heard throughout both lung fields, but no moist râles were heard. Cyanosis of the fingertips was noted. The blood pressure was 144 mm. Hg systolic, and 90, diastolic.

Laboratory examinations revealed a red blood count of 5,410,000; white blood count was 7,350, with 60 per cent neutrophiles, 34 per cent lymphocytes, and 6 per cent eosinophiles. The sedimentation rate was 2 mm. per hour. The Kahn test was negative. Urinalysis showed a specific gravity of 1.007 and was negative for sugar and albumin. There were 1 to 2 white blood cells per high-powered field.

Shortly after admission all former medications were discontinued and the patient was treated with aminophylline, ephedrine, phenobarbital, and oxygen, as needed. After two days of this treatment, she was doing well subjectively. However, occasional asthmatic wheezing continued to be heard and for the next seven days the treatment as outlined was continued. The patient was in good spirits and had no complaints except difficulty in breathing for short periods of time. Between these mild attacks of dyspnea she was asymptomatic. The mild attacks were easily relieved by the administration of oxygen by nasal catheter. Finally, this too became unnecessary and the oxygen was removed from her room. At no time up to this point in her hospital stay did the patient have a fever. Her pulse rate ranged between 80 and 100 per minute and her blood pressure, taken daily, varied between 130 and 145 mm. Hg systolic and 90 and 100 diastolic.

On the ninth day it was decided to see if Benadryl would have any beneficial effect in reducing the residual wheezing. All previous medication was discontinued on the morning

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of June 19, and oral administration of Benadryl prescribed. She was given 100 mg. at noon of that day and 100 mg. again at 4 P.M. One hour after the second dose the nurse noted that the patient was perspiring profusely and was cyanotic. She had also begun to complain of pain in the chest. Benadryl was immediately discontinued. The patient was seen by a medical officer who ordered oxygen by nasal catheter and 50 mg. of Demerol intramuscularly following which she fell asleep.

At 8 P.M. the nurse believed that the patient was semiconscious. She was moaning loudly and although her respirations were labored, her color was good. She was perspiring profusely and the pulse rate was 128 per minute. The medical officer was again called to the ward. He ordered side boards on the bed, ephedrine, gr. ⅜, and luminal, gr. 1½, by mouth. At 10 P.M. the patient was quiet and seemed to be sleeping, but respirations remained labored.

When seen early the next morning the patient was in coma, perspiring profusely, and slightly cyanotic. The bed showed evidence of urinary incontinence. She was extremely dyspneic and was gasping for breath; her respirations were deep and rapid, at a rate of 35 per minute. The skin was cold and clammy and the pulse rate was 140 per minute. However, the heart tones were loud and distinct and the blood pressure was 190 mm. Hg systolic and 140, diastolic. No peripheral venous engorgement was seen and the liver could not be palpated. In the lung fields was heard wheezing with inspiratory and expiratory râles. At this time some moist râles were heard at both lung bases and a moderate amount of frothy expectoration was seen at the mouth. The patient's temperature was 99.6° F. rectally. Neurologic examination revealed the pupils to be round, regular, and equal, neither constricted nor dilated. They reacted bilaterally to light. There was no deviation of the head or the eyes and no apparent facial weakness was seen. She responded to painful stimuli on the extremities by slight movements of the limbs. All extremities were markedly hypotonic and the deep tendon reflexes could not be elicited. The plantar reflex was flexor bilaterally.

Laboratory data at this time revealed the following: Blood sugar was 84 mg. per cent; blood nonprotein nitrogen 34 mg. per cent; and blood urea nitrogen 10.5 mg. per cent. A portable roentgenogram of the chest failed to reveal any changes in the lungs. An electrocardiogram showed a sinus tachycardia, but was otherwise within normal limits.

The patient was placed in an oxygen tent and was given aminophylline, gr. 3¾ intravenously. This failed to produce any change in her condition. She was then treated supportively with 8 cat units of Digiglusin intravenously with no noticeable effect. She was then given 1,000 c.c. of normal saline subcutaneously, 30 c.c. of 50 per cent glucose, and 5 gr. of caffeine sodium benzoate, intravenously. The patient failed to respond to these measures. Her blood pressure gradually decreased and her temperature rose to a terminal fever of 104° rectally. She expired at 5:40 P.M. on June 20.

Post-mortem examination was done five hours after death. There were no unusual external findings. The heart weighed 245 grams. Gross examination of the cardiac chambers, myocardium, and valves showed these structures to be entirely normal. The right, left, and circumflex coronary arteries were without significant changes. The right lung weighed 610 grams and the external surface was smooth, shiny, and grey to black in color. The tissue was moderately crepitant to palpation. On the cut surface a moderate amount of frothy yellow fluid exuded. There were no areas of consolidation or fibrosis, nor any unusual features. Plugs of the larger bronchi were not seen. The left lung was similar to the right lung in all respects. The gastrointestinal tract, the pancreas, spleen, liver, adrenals, kidneys, and generative organs were entirely normal. The brain failed to reveal evidence of any inflammatory alteration or undue pressure. There were no gross or petechial hemorrhages.

Microscopic examination failed to reveal any primary pathologic condition which could have caused this patient's death. There were early changes of a minimal amount of interstitial pneumonia and some congestion of both lungs. Moderate emphysema was present and a few of the smaller bronchi were plugged with mucus. A few glomeruli of the kidneys appeared swollen. The changes in the lungs and kidneys were consistent with the secondary changes that would be seen in a patient who had gradual failure of the vital functions over a twenty-four-hour period terminating in a fatal outcome.

Chemical analysis of the stomach contents failed to reveal the presence of barbiturates, bromides, or other depressant agents or poisons.

The autopsy, then, did not reveal any pathology to indicate the cause of death.

COMMENT

We believe the primary cause of death in this case was severe depression of the central nervous system although other factors undoubtedly contributed to the terminal event. In our opinion, the Benadryl which seemed to precipitate the attack might also have been responsible for this depression.

Most of the side effects of Benadryl are manifested by central nervous system symptoms and signs. Levin[1] lists these: The most prominent are drowsiness, weakness, stupor, narcolepsy, confusion, exhaustion, and collapse.

Similar, but nonfatal, cases have been reported in the literature. Geiger, Rosenfield, and Hartman[2] reported the case of a 26-year-old white woman who took 300 mg. of Benadryl over a period of three days. After an additional 50 mg. she was found cold, unconscious, pale, and pulseless. Her blood pressure could not be obtained. When given 0.5 c.c. of epinephrine, she recovered. The same reaction recurred after an additional 300 mg.; recovery was spontaneous. Willcox[3] reported a patient who became pallid, developed a rapid thready pulse, and collapsed after 200 mg. of Benadryl; recovery was spontaneous. In both of these cases it should be noted that the dosage which precipitated the attacks was small. Our patient received only 200 milligrams.

These cases appeared to be collapse reactions. Our patient, however, developed an unusual hypertension, and there was no evidence of central or peripheral cardiovascular collapse until she became moribund. Although the usual effect of Benadryl is to cause a decrease in blood pressure, other observers[4, 5] have noted hypertension following the use of this drug.

It is likely that the 50 mg. of Demerol and the 1½ gr. of phenobarbital our patient received contributed to the depression of the central nervous system. A synergistic depressive action of these drugs with Benadryl might be postulated.

SUMMARY

1. A case of exacerbation of acute bronchial asthma following Benadryl therapy and terminating in a fatal outcome is reported.

2. Although it cannot be stated categorically that Benadryl alone caused death in this case, the facts do point toward its incrimination.

3. Because of the widespread use of this drug and the possibility of a fatality we believe that greater caution should be exercised in its employment.

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HISTAMINE ANTAGONISTS

XII. Neohetramine, 2-(N-Dimethylaminoethyl-N-p-Methoxybenzyl)-Aminopyrimidine Hydrochloride; Clinical and Pharmacologic Results*

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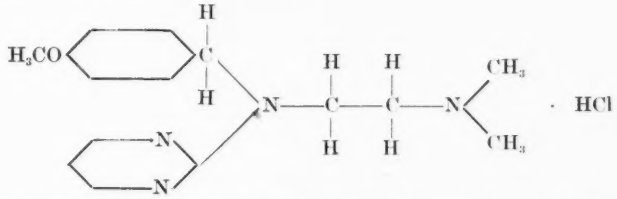
NEOHETRAMINE† is a new drug added to the ethylenediamine series of antihistaminic compounds.[1, 2, 3] The distinguishing feature of its structure is the pyrimidine ring, its formula being:



2-(N-dimethylaminoethyl-N-p-methoxybenzyl)-aminopyrimidine hydrochloride

The characteristic feature of this antihistamine drug is that although its potency of clinical activity is lower than some of the other compounds of the same class, its very low incidence of side actions makes it frequently a drug of choice.

During the past year we have subjected Neohetramine to experimental and clinical investigation and have found that the drug possesess the antihistaminic and antianaphylactic properties typical of the series in general. Guinea pigs given intraperitoneally 3 mg. of Neohetramine per kilogram of animal weight did not die of histamine shock when they subsequently received an intravenous injection of histamine which would produce 100 per cent mortality in unprotected animals. A dose of 1.0 mg. per kilogram produced a mortality of 30 per cent, while a dose of 0.1 mg. per kilogram resulted in 80 per cent mortality from the same amount of histamine.

In another series of experiments, the effect of the drug in preventing dyspnea from histamine aerosol was observed. The protective dose of the drug was given by two methods, by aerosol and intraperitoneally. An aerosol of 4 per cent Neohetramine administered for five minutes at 5 pounds' pressure protected guinea pigs for double their normal time, or longer, when exposed to an aerosol of 0.5 mg. per cubic centimeter of histamine aerolized at 5 pounds pressure. Such protective effect lasted about thirty minutes. Guinea pigs injected intraperitoneally with 10 mg. of Neohetramine per kilogram were able to tolerate ten minutes of continuous histamine aerosolization without dyspnea thirty minutes after the injection. With a dose of 5 mg. per kilogram, although only 30 per cent withstood a ten-minute exposure without dyspnea, all of the

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†Supplied by Nepera Chemical Co., Inc., Yonkers, N. Y.

animals tolerated the histamine for twice their normal control time. The duration of protection by this method was two and one-half hours.

In guinea pigs actively sensitized to horse serum, in which fatal anaphylaxis occurred in 90 per cent of the control group, Neohetramine given in doses of 10 to 20 mg. per kilogram intraperitoneally prior to the shocking doses resulted in 70 per cent survival.

The effect of local application of a solution of Neohetramine on the inhibition of the whealing and flare from locally applied histamine was studied by quantitative titration. This consisted in principle of the following steps: titration of the histamine sensitivity in the subject, application of a selected strength to a series of sites previously treated with Neohetramine, and comparison with other antihistaminics on the same subject at the same time. This procedure was repeated in more than twenty subjects and titrations were compared on the same subjects with other drugs. The results obtained indicate that Neohetramine has approximately 27 per cent of the inhibiting power of Pyribenzamine and 70 per cent of that of Benadryl. In other words, it takes nearly four times the concentration of Neohetramine to produce the same inhibiting effect as Pyribenzamine and about one and one-half times as compared with Benadryl. We do not contend that the method of assay described is an absolute index of the therapeutic efficiency of this drug or any other antihistaminic. It is obvious that other factors, such as gastrointestinal absorption, destruction, and elimination, and perhaps other features enter into the complex of therapeutic potency.

Eight patients took 50 mg. of Neohetramine orally three times daily for a period of four to six months. In weekly and biweekly studies of this group, no significant changes occurred in the blood pressure, blood, or urine.

A group of 148 patients with a total of 184 allergic manifestations was treated with Neohetramine. These conditions comprised seasonal hay fever, perennial rhinitis, seasonal and perennial bronchial asthma, allergic cough, atopic dermatitis, urticaria, and allergic headache. The dose given was 50 or 100 milligrams. For isolated attacks, one dose was used, sometimes followed by a second several hours later. In those instances with continuous symptoms, the medication was administered two to four times daily, preferably after meals. The effect on the symptoms was observed carefully, and, in addition, side

TABLE I. CLINICAL RESULTS WITH NEOHETRAMINE

ALLERGIC DISORDER	DOSE (MG.)	TOTAL PATIENTS	SATISFACTORY RELIEF	PER CENT RELIEVED
Seasonal hay fever	50	65	31	48
	100	30	21	70
Perennial rhinitis	50	34	15	44
	100	14	8	57
Asthma	50	17	2	
	100	6	0	
Urticaria	50	4	3	
	100	3	2	
Atopic dermatitis	50	2	2	
	100	3	0	
Allergic cough	50	3	0	
Allergic headache	50	3	1	

actions were noted. A patient was considered improved if amelioration of symptoms consistently occurred within a reasonable length of time after taking the drug and to a degree deemed sufficient by ourselves and the patient.

The clinical results obtained by the use of 50 and 100 mg. doses of Neohetramine are illustrated in Table I. In asthma, as we had found with other antihistamine drugs, there was no evidence that Neohetramine consistently affected the individual attack or lessened the severity or frequency of repeated episodes.

Side effects occurred less often and were usually less severe than had been our experience with other ethylenediamine antihistaminics. Sedation occurred most commonly, the other manifestations being of the same general nature as obtained with other antihistaminic drugs. The incidence of untoward actions in the 100 patients on a 50 mg. dosage was 9 per cent, while in the forty-eight patients taking a 100 mg. dose the incidence rose to 16 per cent. In the vast majority of these subjects the degree of sedation was slight.

SUMMARY

1. Neohetramine, 2-(N-dimethylaminoethyl-N-p-methoxybenzyl)-amino-pyrimidine hydrochloride, a new antihistamine compound, has been described.

2. This compound is antihistaminic, antianaphylactic, inhibits histamine and antigen whealing, and benefits the symptoms of allergic manifestations, with particular emphasis on seasonal hay fever, nonseasonal allergic rhinitis, and itching dermatoses.

3. As compared with some of the established antihistaminic compounds, larger doses (100 mg. or more) may be required for therapeutic effects.

4. With doses producing a reasonable degree and incidence of therapeutic effectiveness, the incidence and degree of side actions were less than with most other antihistamine drugs.

5. The low toxicity and the fact that individual variabilities enable some persons to respond favorably to some of the antihistaminics while not responding to others make this compound a useful addition to the list of available antihistaminic drugs.

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CONTACT DERMATITIS OF CELERY FARMERS*

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INTRODUCTION

SINCE the latter part of the nineteenth century celery has been grown extensively in Massachusetts. In 1935, a green summer Pascal celery was introduced and because of its superior texture and flavor its culture spread rapidly so that since about 1939 this green Pascal has been grown almost to the exclusion of other varieties.

Dermatitis due to celery has been described. In 1926, Legrain and Barthe,[1] in France, described lesions on the fingers, hands, and forearms of a kitchen gardener. The dermatitis cleared thirteen days after he stopped picking celery, only to return within a few hours after he resumed work. They ascribed the dermatitis to the aromatic oil in the celery. In 1933, Henry[2] in England, described an erythematous, vesicular or papular rash associated with itching in the workers of three factories preparing celery for canning. Within ten days after ceasing work the dermatitis cleared. He assumed that dextrolimonene, the predominant constituent in celery oil, was the causative factor. In 1938, Henry[3] reported further cases of dermatitis in workers preparing celery for canning. About 30 per cent of the workers were affected.

In this country dermatitis among celery farmers did not appear until 1939 when the green Pascal variety was introduced. Since then it has become fairly common among those who handle celery repeatedly and in a few cases the lesions have been severe and incapacitating. The problem of its cause and treatment has become important.

INVESTIGATION

The dermatitis was studied in the workers on fourteen farms, one Chinese food packing plant in the Boston area, and two farms near Sunderland, Massachusetts. As expected, the lesions developed on areas of the skin most exposed. Usually only the hands and forearms were affected, but in a few instances the rash was noted on the chest, abdomen, and legs of the pickers who in summer wore no shirts and rolled up their trousers. The development of the disease was fairly characteristic. At first, there was itching and when the areas were scratched there appeared in twelve to twenty-four hours maculo-papular lesions and then vesicles containing a clear, thin fluid. These vesicles coalesced and later ruptured to release a considerable and troublesome exudate; cracking and lichenification followed. Table I shows an analysis of the personnel involved. Dark-skinned laborers from Jamaica and the Bahama Islands employed on the farms seemed to be immune and only about one-third of the

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TABLE I. INCIDENCE OF CELERY DERMATITIS

	WHITE WORKERS EMPLOYED	WHITE WORKERS AFFECTED		NEGRO WORKERS EMPLOYED	NEGRO WORKERS AFFECTED	
		NUMBER	PER CENT		NUMBER	PER CENT
14 farms (Boston area)	176	67	38.0	50	0	0
2 farms (Sunderland)	17	6	35.3	0	0	0
Chinese Packing Co.	7	4	57	0	0	0
Total	200	77	38.5	50	0	0

whites were affected. In the Chinese packing plant the four sensitive workers developed lesions only when handling native celery. A green celery from California, probably the Utah variety, caused no symptoms. Certain families of workers seemed to be more susceptible than others, as if a familial factor were concerned with the development of sensitivity. Thus, a 53-year-old Italian woman was susceptible to celery. Her daughter, age 27, had the dermatitis, but her son was free from it. However, his child, age 3, developed celery dermatitis after playing in the celery field. On two of the larger farms where twenty or thirty people were employed in harvesting, there was no family relationship among those affected. Meantime, none of the affected workers gave a personal history of hay fever or asthma and in only one subject was there a family history of allergy.

On reviewing the problem, it was necessary to consider four possible causative factors: first, the fertilizers; second, the sprays; third, the bacteria and/or fungi as rotting agents, especially *Erwinia caratovorus* and *Rhizopus nigricans;* and, finally, the constituents of the celery itself.

The fertilizer was easily ruled out. Most farms produced a variety of vegetables and all the land was fertilized with the same materials, but the dermatitis appeared only on farming celery. Incidentally, one person had lesions on handling the celery seeds.

Sprays and their adjuvants, including "stickers," were ruled out. The disease developed in six people in April before there was any use of sprays. On one farm these materials were not used until September, but the dermatitis appeared in July. Bordeaux mixture, the common spray, is widely used on potatoes and other vegetable crops without symptoms.

Most workers reported that dermatitis appeared only when they handled rotten celery at harvest time from July to October. However, the fact that dermatitis appeared in a few cases early in the season in transplanting young plants and at other times when the soft rot celery disease was not a factor, is significant. This celery disease has always prevailed in the celery growing industry. Celery decay appears as a contributing factor in dermatitis, at least in many instances, but only in coincidence with the new variety of celery. The circumstantial evidence is against the importance of the rot.

Finally, the celery plant itself remained as the common denominator. As described above, no trouble was experienced until the new green summer Pas-

cal celery was introduced. Moreover, the amount of handling and the period of exposure definitely influenced the severity of the dermatitis.

TESTS AND RESULTS

Although it was quite obvious that the dermatitis was of the contact type, a few scratch and intradermal tests were made with watery extracts of yellow celery in healthy condition, yellow celery rotted with *Erwinia caratovorus,* yellow celery rotted with the mold Rhizopus, healthy green summer Pascal celery, the same rotted with *Erwinia caratovorus,* and rotted with the mold Rhizopus. In each instance the squeezed juice was sterilized by passing it through a Seitz filter and then it was diluted with carbolized physiologic saline to contain 0.02 mg. and 0.1 mg. total nitrogen per milliliter. As expected, no conclusive positive tests by the scratch and intradermal methods were obtained.

Patch tests were made with various materials applied under cellophane to the normal skin of the forearms. First, seven workers were tested with the celery directly. Small pieces of the stalks of healthy celery and of rotted celery were applied. These tests were read in forty-eight hours. As shown in Table II, three of the seven workers developed itching from the healthy celery and the same three reacted also to the rotted celery. One of them developed vesicles and ulceration.

Second, thirteen workers were tested with ether extracts of the stalks and leaves made as follows: stalks and leaves were separated. Each was ground finely and the ground material was extracted with ether. The ether solution was poured off and filtered and was allowed to evaporate at room temperature in an Erlenmeyer flask. The oily residue was used either in crude form or was diluted 1:10 with persic oil. Patch tests were read in twenty-four hours. Of the thirteen workers tested with the 1:10 dilution in oil, five developed itching under the patch with stalk oil, and one of these showed redness, and another vesicles. Three of the same five workers reacted also to the leaf oil. There was one worker (W. G.) who reacted to the leaf oil but did not react to the stalk oil; there was another (A. B.) who reacted to the stalk but not to the leaf oil.

When the crude oily residue was used in a patch test on nine workers, five reacted with pruritus, four of them showing redness and one of the four, maculo-papular lesions. These particular tests were read in forty-eight hours.

Table II shows the results arranged according to the activities of the workers. Group 1 includes two individuals who had had celery dermatitis before but who did not work with celery in 1947, and so had no dermatitis that year. On them, all tests were negative. Group 2 includes the one worker (C. V.) who wore gloves throughout the season. She had had dermatitis before, but the gloves protected her this year. However, she gave a positive patch test to the diluted stalk oil. Group 3 comprises four workers who had only a mild dermatitis of short duration in 1947, even though they handled celery as much as in former years. No lesions were evident at the time of testing. All tests with the exception of that with the crude rotted celery on one patient were negative.

TABLE II. PATCH TESTS

GROUP	PATIENT	AGE	SEX	HEALTHY CELERY	ROTTED CELERY	STALK OIL 1:10	LEAF OIL 1:10	CONCENTRATED LEAF OIL	DEXTRO-LIMONENE
1. Did not work with celery in 1947	H. D.	34	M	Negative	Negative	Negative	Negative		
	W. W.	17	M			Negative	Negative		
2. Wore gloves—no dermatitis in 1947	C. V.	53	F			Pruritus Erythema	Negative	Negative	
3. Worked in celery; mild dermatitis, none at time of tests	F. T.	31	M	Negative	Negative	Negative	Negative	Negative	Negative
	G. B.	54	M			Negative	Negative		
	J. C.	28	M			Negative	Negative		
	A. D.	34	M	Negative	Maculopapular lesions	Negative	Negative	Negative	Negative
4. Severe dermatitis in 1947	J. C.	32	M	Pruritus Erythema	Pruritus Erythema	Negative	Negative	Negative	
	R. V.	24	F			Pruritus	Pruritus	Pruritus Erythema	Pruritus Erythema Swelling
	R. C.	23	M			Pruritus	Pruritus	Pruritus Erythema Maculopapular lesions	
	A. B.	21	F	Pruritus	Pruritus Vesicles Ulceration (4x7 cm.)	Pruritus Vesicle	Negative	Pruritus Erythema	Pruritus Erythema Swelling
	R. B.	41	F			Pruritus	Pruritus Erythema	Pruritus	
	W. G.	46	M	Negative	Pruritus Erythema	Negative	Pruritus	Pruritus—red indurated area	Pruritus Erythema Swelling
	F. P.	35	M	Pruritus	Pruritus				

Group 4 is the largest: it includes seven workers who were suffering from celery dermatitis at the time of the tests. Four of the seven were tested with the crude juices and all had positive reactions except one worker (W. G.) who responded only to the rotted celery juice. Six of the seven were tested with the diluted oils and five reacted with some variations. It is curious that patient J. C. who reacted to the celery itself showed no reaction to any of the ether extracted materials.

Dextro-limonene has been described by Parry[4] as an essential factor in the oil of fruits and vegetables. Horner,[5] in 1931, and Schwartz,[6] in 1938, inferred that this oil was the sensitizing agent in citrus fruit peels. In 1938, Henry[3] inferred that dextro-limonene was the causative factor in celery dermatitis. Dextro-limonene was tested on our patients.

Patch tests with 100 per cent pure dextro-limonene on the forearms of four people who had never handled celery produced erythema and irritation in ten minutes. When pure dextro-limonene was mixed with mineral oil in various dilutions from 1:2 up to 1:10 and applied as patch tests, the reactions read in twenty-four hours were negative in four normal individuals and in two patients who had had celery dermatitis (F. T. and A. D.). However, on three patients (R. V., A. B., and W. G.) pruritis, erythema, and swelling appeared in twenty-four hours with every test. (Table II.)

DISCUSSION

According to Feinberg[7] the causative factor in plant contact dermatitis is contained in the oil. Our results show that the dermatitis in these celery workers is due to the oil in the plant. The greater fragrance and sharper taste of the green summer Pascal celery suggests that this variety contains a larger amount of oil. The old suspicion that the dermatitis is due to rotted celery is explained by the fact that the disintegration of the celery by soft rot organisms frees the cell juices and provides close contact with the oil.

The variation in the degree of susceptibility of different individuals to the celery oil is striking. One patient had the rash beginning with the planting of the seeds and continuing to the end of the season. Five developed symptoms on transplanting the seedlings to the field and had difficulty throughout the harvest. Most subjects had lesions only for a few weeks during the harvest and remained free the rest of the year. Some could wash celery but developed lesions on harvesting where there is more contact with the plant. Another group, not tested, gave a history of dermatitis for two to five seasons previously, but now they can work without ill effects. Evidently an immunity can be developed. This raises the question of the mechanism of contact dermatitis and its immunology.

As Schwartz[6] says: "Skin sensitizers do not cause lesions on first contact, but they change the skin to make it reactive later." The time required for this change is of interest. Twenty-seven of our patients developed lesions during their first season of handling summer Pascal celery. One patient had no difficulty until the second year; eight remained symptom free until the third year; and three had no trouble until the fifth season.

This history is characteristic of contact dermatitis. Moreover, only about one-third of the workers were affected. The causative factor was not a primary irritant. The results of patch tests suggest that the causative factor is contained in the celery oil. It is interesting that tests were positive only in those who were suffering from dermatitis at the time. Patch tests with dextro-limonene indicate that it may be the cause, or at least one factor, in the celery oil responsible for the dermatitis. Here again the results were positive only in the presence of lesions. The clinical evidence indicates a special dermatogenic quality peculiar to the green summer Pascal celery.

TREATMENT

Treatment might be by elimination, by protection, or by desensitization. The workers could change their jobs, but celery growing is profitable. For protection, gloves are impractical. Henry[2, 3] has found that paraffin oil on the hands and face will protect, but the farmers fear that the oil will soil the celery.

The possibility of desensitization to celery oil is intriguing. Sulzberger[8] and Cooke[9] both state that desensitization is worth a trial in contact dermatitis, even though the mechanism of this therapy is not thoroughly understood. On January 17, 1948, A. B. and W. G. were started on a course of injections of celery oil diluted in persic oil. In June, W. G., after a series of twelve injections at weekly intervals, was up to a dose of 0.50 c.c. of the 1:100 dilution of leaf oil. As yet he has no dermatitis but he has not worked much with celery this year. A. B. has also had twelve injections, but she is up to a dose of only 0.10 c.c. of the 1:1000 dilution intramuscularly. On several occasions she has developed large local reactions with enlarged axillary lymph nodes. She has worked extensively with celery since April 20, 1948. She developed a mild dermatitis on her forearms and hands on April 22, but she was surprised to find that in three days the lesions cleared and in late June she is still free even though she works with celery every day. In other years the lesions persisted once the dermatitis appeared. It is too early to evaluate the worth of this therapy; but if these first two patients really are protected, the fact will be of considerable practical interest.

Green summer Pascal celery is increasing in popularity and its culture is spreading to other celery growing areas. The dermatitis which it causes is an occupational hazard of some importance.

SUMMARY

1. The literature on dermatitis due to celery has been reviewed.

2. Seventy-seven cases of dermatitis in celery workers have been observed.

3. The results of skin tests made by the scratch, intradermal, and patch methods, using various preparations from the celery plant, have been described.

4. The dermatitis is of the contact type and appears to be due to the oil in the celery plant. Dextro-limonene may be a factor in this oil.

5. The methods of treatment are discussed. In a pilot experiment two highly sensitive workers have been protected by injections of the celery oil.

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THE DISTRIBUTION OF RAGWEED POLLEN AND ALTERNARIA SPORES IN THE UPPER ATMOSPHERE

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DAILY pollen counts made by the gravity method on slides exposed near the ground have become routine among allergists. Few have had the equipment or the opportunity to correlate these counts with the distribution and migration of these pollens and molds in the upper atmosphere. The most comprehensive previous studies were made by Durham,[1-3] who exposed slides while traveling in transport planes. His studies established the distribution of pollen at various altitudes and important geographic variations. The present study was made possible by the unrestricted use of our own Piper Supercruiser from which slides were exposed in order to discover the effect of altitude, diurnal and nocturnal variations, and the influence of clouds. All observations were limited to the vicinity of Mitchell Field, Milwaukee, so that the changes in the distribution of pollens involving the influence of time, altitude, and clouds could be effectively studied. The altimeter readings are expressed as the number of feet above sea level. The airport is 676 feet above sea level. The investigation was limited to the distribution of ragweed pollen and alternaria spores, since these particles not only greatly outnumbered all others, but presented morphologic characteristics which made identification simple. The "sky hook" was placed in the slipstream of the plane within three inches of the front window.

Preliminary sampling of the upper atmosphere revealed some surprising discrepancies which were later shown to be due to variations in the speed of the plane. The importance of this factor is shown in Table I. All counts were made by the same technique of the ordinary gravity method on unstained slides and represent the number of granules in one square centimeter. No conversion factors were used.

One would expect that the number of pollen grains on the slide would vary directly with the speed of the plane. However, the enormous increase in the number of particles on the slide with minor increases of speed indicates that other factors beside speed are responsible for the counts obtained.*

Table I shows the importance of maintaining a constant speed while collecting samples. Therefore, an airspeed of 90 m.p.h. was arbitrarily selected for all collection of particles, as this speed could safely be maintained even in the turbulent atmosphere encountered in and near cumulus clouds. All subsequent counts were based on five-minute exposures.

EFFECT OF ALTITUDE AND FAIR WEATHER CUMULUS CLOUDS

An analysis of the findings shown in Table II indicates that the greatest concentration of pollen and molds occurred at 3,500 feet with a decrease

*Further study is necessary to determine the effect of air compression in front of the slide, as well as the difference in behavior of the heavier spherical ragweed pollen grains and the lighter bowling pin-shaped alternaria spores.

TABLE I. FIVE-MINUTE EXPOSURES OF SLIDES AT 2,500 FEET

REVOLUTIONS OF PROPELLER PER MIN.	INDICATED AIR SPEED M.P.H.	RAGWEED (R)	ALTERNARIA (A)	RATIO R/A
2,250	110	6,000	4,700	1.3
1,930	90	1,200	1,800	.7
1,875	70	740	900	.8
1,950	50	740	1,000	.7
24-hour gravity slide		150	33	4.5

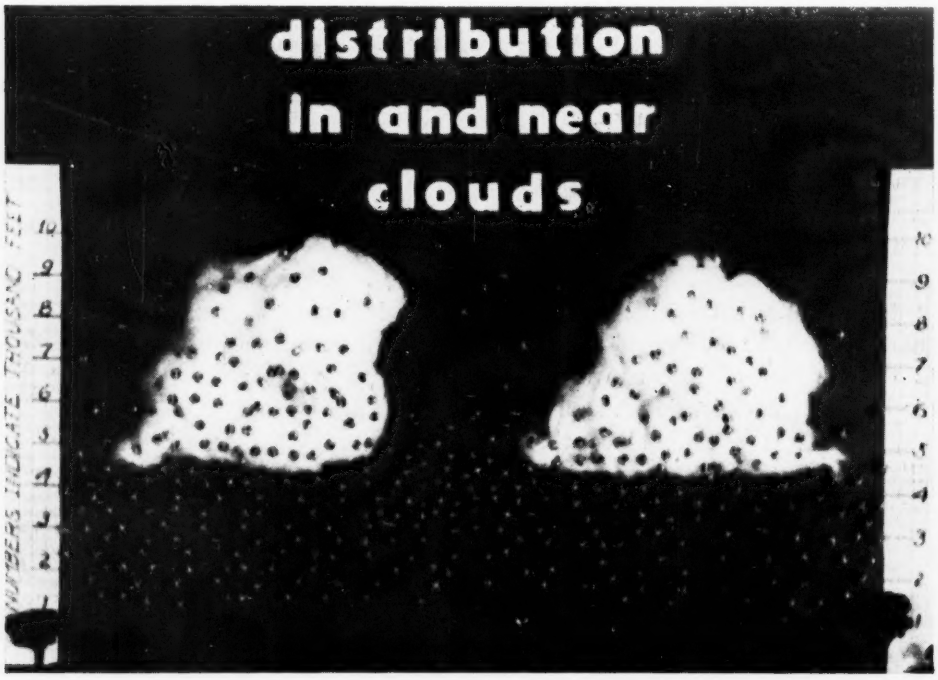

Fig. 1.—Note pollen and spore granules in and adjacent to clouds in contrast to the space above and below these concentrations.

TABLE II. COUNTS MADE IN CLEAR AIR AND IN CUMULUS CLOUDS (SEPT. 1, 1947; WIND, WNW; 25 M.P.H.; SCATTERED CUMULUS 5,500 FEET TO 10,000 FEET; 24-HOUR GRAVITY SLIDE RAGWEED, 100; ALTERNARIA, 5)

ALTITUDE	TIME (P.M.)	IN CLEAR AIR AWAY FROM CLOUDS RAGWEED—ALTERNARIA	TIME (P.M.)	ABOUT ½ TIME IN CLOUDS RAGWEED-ALTERNARIA
9,500			2:20	8-2
8,500	2:00	0-0		
7,500	1:40	18-2	2:40	800-100
6,500	1:25	85-8		
5,500	1:10	175-125	2:50	1,600-300
4,500	1:00	1,100-125		Below clouds
3,500	12:50	1,700-375	3:00	1,300-75
2,500	12:40	1,450-325		
1,500	12:30	1,000-225	3:10	1,650-150

in number of particles at higher and lower altitudes. However, the cumulus clouds and surrounding atmosphere contained many times the number of particles found in the clear air further from the clouds. The reported

counts in the clouds are actually much lower than they would have been if the entire five minutes could have been spent in the clouds. Continuous flying through the clouds is impracticable, so the figures represent the compromise of flying through clouds about one-half of the time. These fair weather cumulus clouds are caused by the rising of heated moist air to an altitude where the dew point and temperature meet and condensation occurs. The turbulence in the clouds is associated with the liberation of heat as condensation proceeds. The cloud itself then acts as a huge chimney drawing

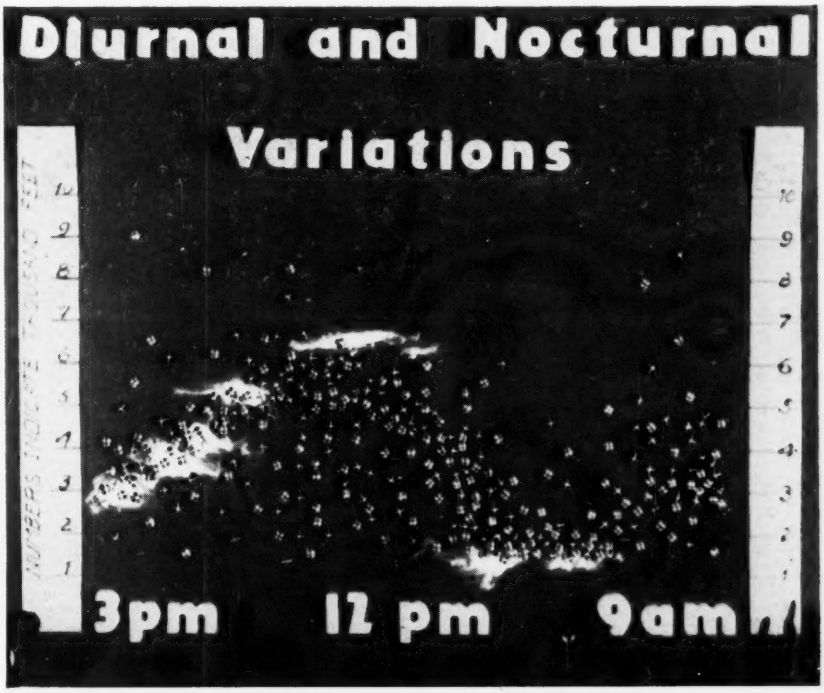

Fig. 2.

pollen from the lower atmosphere and lifting it far above its usual altitude. It is also probable that some of the condensation of moisture in the clouds takes place on the pollen or mold granule, the granules themselves serving as condensation nuclei without which cloud formation is impossible. Regarding this possibility it is an interesting finding that slides exposed in the clouds frequently revealed pollen grains that were attached to or surrounded by globules of water.

DIURNAL AND NOCTURNAL VARIATIONS

Table III shows the actual counts obtained at various altitudes at the indicated times of day or night. Since the time required for collection of pollens and molds prevented a simultaneous determination of the counts at various altitudes, there are necessarily many gaps in Fig. 2. The gaps are filled in according to the trends which have been established in Table III.

TABLE III. DIURNAL AND NOCTURNAL VARIATIONS (SEPT. 19-20, 1947; WIND, SE; 8 M.P.H.; GRAVITY SLIDE COUNTS—SEPT. 19: RAGWEED, 75, ALTERNARIA, 12; SEPT. 20: RAGWEED, 25, ALTERNARIA, 10)

ALTITUDE									
9,500		R/A, 5/2 Above stratus clouds 8:00 P.M.	R/A, 0/0 10:25 P.M.						
8,500									
7,500		R/A, 150/130 In stratus 8:15 P.M.	R/A, 5/0 10:35 P.M.	R/A, 0/0 1:00 A.M.	R/A, 0/0 Calm 4:10 A.M.	R/A, 0/0 6:00 A.M.			
6,500									
5,500	R/A, 75/25 3:40 P.M.	R/A, 450/390 8:20 P.M.	R/A, 140/200 10:45 P.M.	R/A, 85/150 1:07 A.M.	R/A, 150/120 Thin stratus 4:15 A.M.	R/A, 0/1 6:10 A.M.	R/A, 7/3 7:00 A.M.		
4,500	R/A, 125/175 3:47 P.M.	R/A, 205/95 8:30 P.M.	R/A, 235/215 10:55 P.M.	R/A, 150/170 1:15 A.M.	R/A, 100/120 4:25 A.M.	R/A, 3/1 6:20 A.M.	R/A, 75/210 7:07 A.M.	R/A, 210/75 11:15 A.M.	R/A, 310/200 11:40 A.M.
3,500	R/A, 225/200 4:00 P.M.	R/A, 300/190 8:35 P.M.	R/A, 160/260 11:00 P.M.	R/A, 160/280 1:25 A.M.	R/A, 87/310 4:32 A.M.	R/A, 3/0 6:30 A.M.	R/A, 150/220 7:15 A.M.	R/A, 520/270 11:20 A.M.	
2,500	R/A, 470/170 Hazy 4:06 P.M.	R/A, 320/220 8:45 P.M.	R/A, 360/300 11:10 P.M.	R/A, 120/220 1:30 A.M.	R/A, 125/190 4:40 A.M.	R/A, 75/16 6:40 A.M.	R/A, 45/50 7:22 A.M.	R/A, 310/200 11:40 A.M.	
1,500	R/A, 125/50 4:20 P.M.	R/A, 230/165 8:50 P.M.	R/A, 160/290 11:20 P.M.	R/A, 220/210 1:45 A.M.	R/A, 240/220 4:45 A.M.	R/A, 250/625 Ground fog 6:45 A.M.	R/A, 110/210 7:30 A.M.	R/A, 320/230 11:50 A.M.	

In addition, the maximum concentrations have been exaggerated in order to demonstrate more clearly the variations depending on the time of day or night. The data indicate that the level of maximum concentration rose from early afternoon until about 8 P.M. when the particles slowly fell until dawn, at which time there was ground fog. An analysis of these findings seems to indicate that the convection currents during the day and early evening are responsible for the lifting of the particles to high altitudes, and that the particles then sink as the ground cools off. Fig. 2 also indicates a tendency for the particles to be most numerous in haze and ground fog. The importance of these observations is that they help explain the well-known fact that pollenosis is usually at its worst in the early morning hours.

Some interesting comparisons of the number of particles obtained by the airplane method with the gravity method of counting are worthy of mention. The present study indicates that during the daytime at 2,500 feet and 90 m.p.h. as much ragweed is collected in about thirty-five seconds as can be collected in twenty-four hours by the gravity method. At night, at 2,500 feet, it takes as much as eight minutes to collect an amount of pollen equaling the twenty-four hour gravity count. Alternaria spores, on the other hand, may be collected during daylight hours at a rate indicating that ten seconds of flying under the conditions established for ragweed counts equals a twenty-four hour gravity count. At night, however, about one and one-half minutes of flying are necessary to equal the twenty-four hour gravity count.

Further study is expected to explain these findings. Plans for the future are concerned with a correlation of meteorologic data with upper air pollen counts, with the hope of obtaining information which may be of value in prophesying pollen counts on a twenty-four hour basis.

SUMMARY

1. Counts of ragweed pollen and alternaria spores in the upper atmosphere were made during flight.

2. The greatest concentration of pollen occurred at 3,500 feet.

3. Cumulus clouds and surrounding atmosphere contained many times the number of particles found in clear air away from the clouds.

4. The level of maximum concentration of particles rose from early afternoon until about 8 P.M. when it fell slowly until dawn.

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AN UNUSUAL CASE OF HYPERSENSITIVITY TO COLD COMPLICATED BY PAROXYSMAL DIARRHEA*†

CAPTAIN JOHN P. MCGOVERN, MEDICAL CORPS, ARMY OF THE UNITED STATES

AN UNUSUAL case of hypersensitivity to cold complicated by paroxysmal diarrhea, together with a discussion, is presented herewith.

CASE REPORT

J. B. T., a 33-year-old white male dentist, came to the clinic with the chief complaint that he had been "allergic to cold for several years." He had been free from allergic manifestations other than a hypersensitive reaction to poison ivy for which he was hospitalized twice at the ages of 16 and 21.

The first sign of hypersensitivity to cold occurred in the summer of 1941 at the age of 28. While canoeing he fell into cold water up to his hips. During the return home he noticed hives and itching on the exposed areas. Both symptoms disappeared within one-half hour of exposure.

In September of the same year the patient was inducted into the Navy. Soon thereafter, while vacationing at a beach, he had a second reaction. He had been swimming for approximately fifteen minutes and about five minutes after coming out of the water he became very dizzy and had an inordinately great desire to defecate. Scotomata were associated with these symptoms and soon everything "became black." He had one large, forceful, watery, diarrheal stool, without blood. Itching and redness of the skin followed this. That winter, when exposed to cold weather, he noticed hives, itching, and redness over the hands, neck, and face. There were no generalized reactions. Holding cold drinks caused edema of the fingers; ice cream and other cold substances caused itching in the mouth with moderate swelling of the tongue and lips. He consulted several physicians who were not acquainted with this symptom complex and who offered palliative measures only.

The next summer the patient went swimming several times without ill effects. In July, however, after swimming approximately thirty minutes, he became dizzy and had scotoma and diarrhea as before. As he was unable to walk this time, he was carried to an automobile and driven to a Naval dispensary. A blood pressure reading taken at this time was 70/?; the pulse was weak and rapid. No hives were noted. He was placed in the shock position and completely recovered within an hour without aid of medication.

The next two years the patient served aboard ship in the Pacific Theater. During this period he was not exposed to cold.

In 1946 he returned to the United States and on first exposure to cold weather noticed hives, pruritus, and redness on the exposed areas. At Christmas time, following exposure for one hour, within five minutes after returning to the warmth of the house he had one watery diarrheal stool without blood. He also had the usual reaction on the exposed parts. He has continued to have reactions to cold environment for the past six months. No gross hemoglobinuria followed any of these attacks.

There was no family history of asthma, hay fever, eczema, or other allergic diseases.

The patient's past history was entirely negative. The patient was well developed and slightly obese. The physical examination was otherwise essentially negative. All relevant laboratory examinations were negative.

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*From the Department of Physical Medicine, Veterans Administration Hospital, Richmond, Va.

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Special Studies.—Small pieces of ice were placed upon the arm and chest for five minutes. Redness appeared within one minute after the application, with local circumscribed areas of edema beginning about ninety seconds after removal of the ice. The appearance time of the hives could be speeded by placing an infrared lamp over the exposed area following removal of the ice. At no time, following many tests, did pseudopodia form.

Following immersion of the hand in water at 48° F. for three minutes, redness, itching, and swelling occurred in that order. There were no demonstrable generalized reactions when a tourniquet was placed on the arm before exposure and released two minutes following exposure.

Intradermal skin tests with 0.05 c.c. and 0.1 c.c. of 1:1000 solution of histamine phosphate were within normal limits, the wheals being small and without pseudopodia.

Passive transfer tests (Prausnitz-Küstner reaction) were tried several times and on each occasion were negative. The patient's serum was cooled at 50° F. for three minutes for two tests and was injected without previous cooling two other times without reaction.

To demonstrate histamine activity a study with Benadryl hydrochloride was performed. The first day 100 mg. of Benadryl was administered subcutaneously followed in thirty minutes by immersing the hand in water at 48° F. for three minutes and placing a piece of ice on the forearm. The reactions were exactly comparable to those elicited without Benadryl. The procedure was repeated on alternate days giving the Benadryl one, two, and three hours before the cold applications. In no instance did the drug modify the reaction to cold.

Treatment.—Treatment was given twice daily, including Saturday and Sunday, for two months. It was based on the principle of desensitization to the offending substance assumed to be liberated on exposure to cold. One hand was immersed in water at 48 to 50° F. for two minutes, alternating hands for each exposure. The intensity of the reaction became less on the fifth day of treatment and at the end of one week there was marked reduction in the erythema, pruritus, and swelling. The exposure was increased to three minutes with the reaction remaining minimal. After two weeks of treatment with three-minute exposures no reaction was noticeable. Four-minute exposures then failed to excite response and after one week five-minute exposures were begun, also without demonstrable reaction.

Following this the patient went north on vacation but faithfully kept up his treatments with the equipment given him. While he was riding one evening during a snow storm, his automobile stalled and he was obliged to get out into the cold and push. Reentering the car, he noticed itching and swelling of the exposed parts. During this attack he lost whatever desensitization the treatments had effected for his reaction to a two-minute hand immersion at 48 to 50° F. was as strong as when treatment was begun. Another program of desensitization was initiated but was interrupted when the patient was transferred to California. He has had no generalized reactions during the past year of residence in this climte.

DISCUSSION

The etiology of this symptom complex remains an enigma. Although several cases of altered reactivity to purely physical stimuli were reported earlier, it remained for Duke[1, 2] to suggest the relationship between allergic disease and the allergic-like manifestations caused specifically by the topical application of a physical agent. Majority opinion would disavow that this is a true allergic process involving an antigen-antibody reaction. Evidence has been presented[3] explaining this phenomenon on the basis of a histamine reaction. The absence of a hypersensitive response to histamine and the failure of Benadryl hydrochloride to modify the reaction to cold in our patient were interesting in this respect. The observations did not coincide with those of Feinberg and Friedlaender[4] who, in a preliminary report, recently found that Benadryl was effective for the control of cold urticaria in a patient. Abramson[5] demonstrated to his satisfaction that a transient case of cold allergy was due to psychic conflict.

If suspected, the diagnosis of hypersensitivity to cold can be made simply by the cold tests described. In some instances the reaction may be augmented if the exposure to cold is followed by heating of the part. Although several dramatic cures have been reported, the treatment of hypersensitivity to cold is difficult in most cases. Treatment consists of the immediate alleviation of the attack if it be generalized and rendering the patient insensitive to further exposures. For the acute attack an application of heat often dissipates the symptoms as does the subcutaneous injection of adrenalin chloride solution. A few cures within several weeks have been reported by desensitization with cold applications and by histamine desensitization.[3] In our patient progressive exposure to cold seemed to be of temporary benefit only.

SUMMARY

1. An unusual case of hypersensitivity to cold is presented.

2. Both local and generalized symptoms were observed with paroxysmal diarrhea complicating the systemic reaction on three occasions.

3. Severe systemic reactions were observed following swimming.

4. Evidence is presented that this symptom-complex may not be due to a hypersensitive reaction to histamine, since Benadryl hydrochloride failed to modify the response to cold.

The chemical analyses were performed by David H. Miller, Biochemist at the Veterans Administration Hospital.

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American Academy of Allergy

FIFTH ANNUAL MEETING OF THE ACADEMY
CHALFONTE-HADDON HALL, ATLANTIC CITY, N. J.
DEC. 6, 7, 8, 1948

Program

Monday, December 6, Vernon Room, Lounge Floor, Haddon Hall

9:00 A.M.

Chairman of Scientific Session
Walter W. Winkenwerder, M.D., Assistant Professor of Medicine
Johns Hopkins University Medical School, Baltimore, Maryland

"Therapeutic Bronchoscopy in Bronchial Asthma," George L. Waldbott, M.D., Detroit, Michigan.

"The Use of Vaso-Constrictors and Vaso-Dilators in Asthma," Alan Cazort, M.D., Little Rock, Arkansas.

"An Approach to the Problem of 'Epinephrine Fastness,'" Fredrick F. Yonkman, M.D., and Frank L. Mohr, M.D., Research Department, Ciba Company, Summit, New Jersey.

Intermission

"Local Nasal Therapy With Pyribenzamine in Non-Seasonal and Seasonal Hay Fever," Emanuel Schwartz, M.D., Brooklyn, New York.

"Iontophoresis of Pyribenzamine Hydrochloride in Nasal Allergy," Meryl M. Fenton, M.D., Detroit, Michigan.

"Nasal Use of Antibiotics in Respiratory Allergy," Henry D. Ogden, M.D., Florence Lydia Evans, Ph.D., and J. D. Kelly, M.D.; New Orleans, Louisiana.

2:00 P.M.

Chairman of Scientific Session
Harry L. Rogers, M.D., Chief of Allergy Clinic
Jefferson Medical College, Philadelphia, Pennsylvania

"Fixed Anaphylactic Sensitization," Jerome J. Sievers, M.D., Gordon E. Morey, M.D., and Max Samter, M.D., Chicago, Illinois.

"Experimental Sensitization With Food Dyes and Cross Sensitization to Paraphenylenediamine," R. L. Mayer, M.D., Research Department, Ciba Company, Summit, New Jersey.

The Harry H. Donnally Memorial Lecture

"The Immunology of Virus Diseases," Thomas H. Francis, M.D., Professor of Public Health, Univ. of Michigan Medical School, Ann Arbor, Michigan.

Intermission

"Clinical and Experimental Studies With Orthoxine in the Treatment of Bronchial Asthma," John J. Curry, M.D., Job E. Fuchs, M.D., and Samuel E. Leard, M.D., Boston, Massachusetts.

"Hypersensitivity to Mercuhydrin With Positive Skin Test," Maxwell L. Gelfand, M.D., New York City, New York.

"Testing for Hypersensitiveness by Electrophoresis," Abraham Walzer, M.D., and Harry A. Golan, M.D., Brooklyn, New York.

8:00 P.M.
ANNUAL BUSINESS SESSION

Tuesday, December 7, Vernon Room

9:00 A.M.

Chairman of Scientific Session
M. Coleman Harris, M.D., Associate Clinical Professor of Medicine
College of Medical Evangelists, Los Angeles, California

"An Evaluation of the Effect of Radiation on the Naso-Pharynx in Asthmatic Children," Victor L. Cohen, M.D., Buffalo, New York.

"Experimentally Induced Species Specific Insulin Resistance in the Rabbit," William Franklin, M.D., and Francis C. Lowell, M.D., Boston, Massachusetts.

The Robert Ward Lamson Memorial Lecture

"An Experimental Approach to Psychosomatic Phenomena in Rhinitis and Asthma," Thomas H. Holmes, M.D., Helen Goodell, M.D., Stewart Wolf, M.D., and Harold G. Wolff, M.D., Professor of Medicine, Cornell University Medical College, New York City, New York.

Intermission

"A Statistical Study of the Emotional Component in Allergy: Its Relationship to the Age and Sex Distribution of 6,000 Cases," Milton B. Cohen, M.D., and Lewis E. Abram, M.D., Cleveland, Ohio.

"Group Psychotherapy as an Aid in the Treatment of Allergic Symptoms," Hyman Miller, M.D., and Dorothy W. Baruch, M.D., Beverly Hills, California.

"Observations on the Effect of Adrenocorticotropic Hormone on a Case of Loeffler's Syndrome and a Case of Tropical Eosinophilia," P. Herbert, M.D., and Bram Rose, M.D., Montreal, Canada.

2:00 P.M.

Chairman of Scientific Session
Frank R. Menagh, M.D., Chief of Department of Dermatology
Henry Ford Hospital, Detroit, Michigan

"Factors Influencing Reagin Formation in Experimental Human Sensitization to Ascaris Lumbricoides Antigen. IV. The Influence of a Previous Sensitization on Rate of Reagin Formation," Eloise W. Kailin, M.D., Elinor A. Rossbach, M.D., and Matthew Walzer, M.D., Brooklyn, New York.

"The Effect of Pyribenzamine and/or Rutin on Inverse Anaphylaxis, Forssman Anaphylaxis, and Active Anaphylaxis," Carl E. Arbesman, M.D., and Erwin Neter, M.D., Buffalo, New York.

Presidential Address
Karl D. Figley, M.D., Toledo, Ohio

Intermission

"Air-Borne Allergens in the National Parks," Oren C. Durham, Ph.D., Chicago, Illinois.

"Special Studies of Antihistaminic Drugs," Alex S. Friedlaender, M.D., Sidney Friedlaender, M.D., and J. M. Vandenbelt, Ph.D., Detroit, Michigan.

"Asthma Due to Halogens," Robert Lovell, M.D., and John M. Sheldon, M.D., Ann Arbor, Michigan.

6:00 P.M. *Cocktails, Rutland Room, Upper Lounge, Haddon Hall*

7:00 P.M. *Annual Banquet, Vernon Room, Lounge Floor, Haddon Hall*

Address: "Tomorrow's Food and Its By-Products," Dr. William J. Hale, Consultant to Dow Chemical Company, Midland, Michigan.

Wednesday, December 8, Vernon Room

9:00 A.M.

Chairman of Scientific Session
Ernest L. MacQuiddy, M.D., Attending Physician
University of Nebraska College of Medicine Hospital, Omaha, Nebraska

"Further Observations on Prevention and Treatment of Respiratory Infections in Allergic Patients," Samuel J. Prigal, M.D., New York City, New York.

"Capillary Permeability Studies With the Dermofluorometer," Leo H. Criep, M.D., and Macy Levine, M.D., Pittsburgh, Pennsylvania.

"A Critical Review of the Problem of Bacterial Allergy With Experimental Reports," Oscar Swineford, Jr., M.D., and James Holman, M.D., Charlottesville, Virginia.

"Studies on Soluble Antigen-Antibody Complexes. I. The Specific Interaction of Antibody With Small Molecules," Herman N. Eisen, M.D., and Fred Karush, Ph.D., New York City, New York.

"The Chemical Isolation and Biological Assay of Extracellular Antigenic Fractions From Pathogenic Fungi," Edmund L. Keeney, M.D., and Nils Erickson, Ph.D., San Diego, California.

"The Use of Ragweed Ointment in Determining Seasonal Variation of Ophthalmic Sensitivity," Maurice H. Shulman, M.D., Boston, Massachusetts.

2:00 P.M.

Chairman of Scientific Session
Wyndham B. Blanton, M.D., Professor of Clinical Medicine
Medical College of Virginia, Richmond, Virginia

"Vital Capacity Studies to Differentiate Types of Bronchial Asthma," Sidney W. Jennes, M.D., Waterbury, Connecticut.

"Vegetable Gums by Ingestion in the Etiology of Allergic Disorders," H. Harold Gelfand, M.D., New York City, New York.

"Summer Asthma Mysteries," Howard C. Leopold, M.D., Philadelphia, Pennsylvania.

Intermission

"Periarteritis Nodosa—Experimental Production by Streptococcus Toxin," Leo H. Criep, M.D., and Lloyd Mayer, M.D., Pittsburgh, Pennsylvania.

"Allergic Manifestations of the Eye and Surrounding Structures," Samuel J. Taub, M.D., Mary Jane Fowler, M.D., Benjamin R. Gutow, M.D., Robert E. Miller, M.D., and Robert G. Taub, Chicago, Illinois.

"Hyposensitization Therapy in Patients With Local and Constitutional Reactions to Insulin," Merle W. Miller, M.D., and Joseph T. Beardwood, M.D., Philadelphia, Pennsylvania.

THE FOLLOWING PAPERS WILL BE READ IF TIME PERMITS:

"Allergic Toxaemia and Fatigue Due to Food Allergy," Albert H. Rowe, Oakland, California.

"Further Light on the House Dust Allergen," Marion T. Davidson, M.D., Birmingham, Alabama.

"Allergy: Its Fundamental Aspects," J. Mercer Anderson, M.D., Salt Lake City, Utah.

In Memoriam

PHILIPP SCHONWALD

Philipp Schonwald died at his home in Seattle on December 20, 1947, ending six years of semi-invalidism, during which he bravely continued research and practice.

Dr. Schonwald was born and educated in Vienna. He was graduated from the University of Vienna in 1904 and became interested in the study and treatment of tuberculosis and other chest diseases. A long-felt desire to come to the United States prompted him to leave his post as chief of the medical staff of a large sanitarium. He came to Seattle in 1921 as an established chest specialist.

Dr. Schonwald early realized that many nontuberculosis chest diseases were of an allergic nature. This led to pioneer studies in allergy and related fields, which he carried on to the last. He was an early contributor to the investigation of the relationship of molds and fungi to allergy. Later he conducted research in the field of antibiotics. In recent years he published several papers concerning original observations about these substances as related to allergy. At the time of his death, he was observing soil and air-borne bacteria and their possible relationships to medicine and allergy.

Six years ago, Dr. Schonwald suffered a stroke which resulted in a left hemiplegia. Although seriously disabled, he continued to practice part of the time and to work constantly on research problems. During a portion of the war, he was the only allergist serving his community. His mind was keenly alert despite the physical deterioration and pain.

Dr. Schonwald was a Fellow of the American Academy of Allergy, the American College of Allergists, the American College of Chest Physicians, the American Academy of Tuberculosis, and the American College of Physicians. He was a member of the American Trudeau Society and the International Correspondence Society of Allergy. His cultural accomplishments were many; he spoke several languages and was well known as a painter and a violinist.

Furthermore, he was widely noted as a philanthropist and humanitarian. The loss of Dr. Schonwald will be keenly felt by his community.

ALEXANDER R. ALTOSE.

GEORGE CHAMBERS ANGLIN

George Chambers Anglin died at his home in Toronto on April 14, 1948, from coronary thrombosis.

Dr. Anglin was born in Cork, Ireland, in 1890. He came to Canada in 1907 and graduated in Medicine from the University of Toronto in 1914. At the outbreak of World War I he was in England beginning postgraduate work

but returned to Canada and joined the Royal Canadian Army Medical Corps. He was invalided home after three years of service and began the practice of internal medicine in Toronto. He became interested in pulmonary tuberculosis and respiratory diseases in general and joined the Chest Clinics of the Toronto Western Hospital and the Christie Street Military Hospital.

In World War II he became a consultant in diseases of the chest to M.D. 2 and to the Royal Norwegian Air Force in Toronto. He received the Haakon VII Medal of Liberation from the King of Norway in recognition of his services. At the time of his death, he was serving as Chief of the Chest Clinic of the Department of Veterans Affairs in Toronto.

Dr. Anglin became a Fellow of the American College of Physicians in 1931. He was a member of the Laennec and Trudeau Societies, the American Academy of Allergy, the American College of Allergists, the American College of Chest Physicians, and a diplomate of the American Board of Internal Medicine.

Possessed of a genial personality and impelled by a natural interest in people, Dr. Anglin was also endowed with unusual ability and as a result he reached a high level in the field of medicine and was a strong influence in the improvement of medical practice in this country.

H. K. Detweiler.

CLARENCE KRAUS WEIL

Occasionally, a member of the medical profession passes on and leaves a mark, which was not fully recognized during his lifetime. Such is the case of Clarence Kraus Weil.

He was born in Alabama in 1900. After graduating in Medicine from Columbia University in 1923, Doctor Weil returned to his native city to practice surgery and medicine.

Because of an outside hobby in botany, he became interested in the field of allergy; particularly, as it concerned pollinosis. In 1925, he was among the pioneer students of allergic phenomena. Being a keen observer, and an even more keen analyst, he rapidly recognized the role of allergy in the practice of medicine, and by his own ingenuity and perseverance, became a recognized authority in the South, in the field of allergy.

Among his early observations were the studies made on pecan pollinosis, and he was one of the first to make a pollen survey in the southern states. He also reported the first case of tanytarsus insect allergy.

Locally, he was an organizer of medicine. He was active in the promotion of hospital facilities; in the development of young medical men; in the progress of medicine as practiced in this area. In addition to being a leading physician and clinician, he was an active leader in many community affairs.

He volunteered in World War II, and reached the rank of Lieutenant Colonel in the Medical Corps.

His sudden death is a great loss to the field of medicine in Montgomery, Alabama.

He is survived by his wife and two daughters.

Norman Van Wezel.

SAMUEL HUMES WATSON

Samuel Humes Watson died at his home in Tucson, Arizona, on February 5, 1948, after a lingering illness. The cause of death was cerebral thrombosis.

Dr. Watson was born in 1877 in Vinton, Iowa, the son of Peter Wesley Watson and Blanche Hewes Watson. He attended Cornell College at Mt. Vernon, Iowa. He received his medical degree from Rush Medical College in 1899. He began the practice of medicine in Blairstown, Iowa. It was there that he met Jane Shreeves and they were married in 1906. He came to Tucson in 1911 suffering with tuberculosis and there he fully recovered his health.

It is with medicine, particularly allergy and tuberculosis, in Arizona and the Southwest, that his name is associated. Like his late associate, Dr. Charles S. Kibler, he was a pioneer in allergy. These two phases of medicine, tuberculosis and allergy, held his attention throughout the remainder of his life. The one he had conquered by regaining his health. The other was a challenge to his keen and inquisitive mind for, after regaining his health from tuberculosis, he found that he had asthma. With his characteristic zeal and enthusiasm he tackled this problem and soon found himself launched into the field of allergy in its infancy.

Until 1918 he was Medical Director of the Tucson, Arizona, Sanatorium. In 1918, with Dr. Meade Clyne, he formed the Tucson Clinic, which became one of the leading groups in the Southwest. About the same time he established the first clinical laboratory in Tucson.

Other appointments in Tucson which he held were: Medical Director, St. Luke's in the Desert; Physician in Chief, Barfield Sanatorium; Attending Physician, Chief of Staff, Chairman, and Member of the Executive Committee, St. Mary's Hospital and Sanatorium; Medical Director of the Anson Rest Home for Tuberculosis.

He served as President of the Pima County and the Arizona State Medical Associations, and the Arizona Anti-Tuberculosis Association; Vice-President of the American Association for the Study of Allergy; Director of the National Tuberculosis Association.

In addition to membership in the Academy of Allergy he was associated with the American Sanatorium Association, the Medical and Surgical Association of the Southwest, the American College of Physicians, the American Medical Association, the American Trudeau Society, the American College of Chest Physicians, and the American Association of Tuberculosis Physicians. He was a Diplomate of the American Board of Internal Medicine with Certification in Tuberculosis and Allergy.

He made many contributions to medical journals in the fields of both allergy and tuberculosis.

The passing of Dr. Watson was a great loss to the medical profession and to his community. His was a rare combination of judgment, uncompromising integrity, loyalty, understanding, and devotion to his chosen profession. The Academy has lost a devoted friend and a respected colleague. We extend our deepest sympathy to his family.

W. B. STEEN.

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